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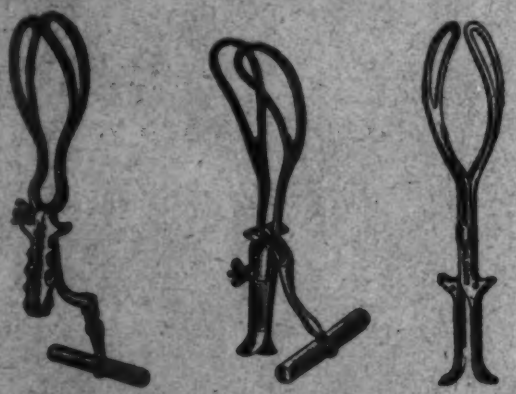

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LONDON SATURDAY MARCH 13 1954

A CRITICAL ANALYSIS OF CATION-EXCHANGE THERAPY

BY

A. G. SPENCER, M.D., M.R.C.P.

AND

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It is now established that cation-exchange resins are sometimes an effective adjuvant to a low-salt diet in the treatment of oedema. The early hope that the use of ion-exchange resins would allow patients with cardiac oedema to take a more liberal diet and an increased intake of salt has not been realized (Greenman *et al.*, 1953). The main advantages now appear to be these: first, resin treatment may succeed when other methods have failed; secondly, by preventing the absorption of sodium and the reaccumulation of oedema fluid, the patient may be spared much discomfort, and the periodic use of mercurial diuretics becomes unnecessary.

It is often difficult to assess the contribution of ion-exchange resins to the successful results that have been reported. This is because a preliminary control period has not always been obtained, and because resin therapy has been used simultaneously with other forms of treatment, such as mercurial diuretics (Elkinton *et al.*, 1952), A.C.T.H. (Greenman *et al.*, 1951b), and abdominal paracentesis (Payne and Wilkinson, 1951). In addition, the published results show a great variation in the response of individual patients; in some a negative sodium balance was not obtained (Danowski *et al.*, 1951; Klingensmith and Elkinton, 1952), and it seems certain that these patients failed to benefit from ion-exchange therapy. Serious complications such as acidosis and potassium depletion are common to many reports (Dock and Frank, 1950; Greenman *et al.*, 1953) and were encountered in the present series. Although resins are now available in a palatable form, the large bulk that must be ingested, the relatively high cost, and the close chemical control that is necessary during treatment are practical reasons for restricting their use. Moreover, the response of many patients to rest in bed, a low-salt diet, digitalis, and mercurial diuretics is so good that no other treatment is needed.

It is clear that the selection and management of patients require considerable experience and care. Despite an abundance of biochemical data, there is little information to guide the practitioner in the safe and effective use of cation-exchange resins. The purpose of the present paper, therefore, is to present and analyse the results obtained over the past three years with special reference to the selection of patients, the methods by which dangerous complications can be avoided, and the most effective use of the resins now available.

Material and Methods

Observations were made on 39 patients with peripheral oedema due to cardiac (30) or renal (9) disease (Table II). The patients were not specially selected, and included those with all degrees of oedema from gross anasarca to minimal ankle-swelling; but many (32) had persistent chronic oedema which had failed to respond to intensive treatment by all the standard methods.

The patients were treated in bed on a constant regime, taking a low-salt diet with a restricted fluid intake of 40 oz. (1,140 ml.) a day. Six diets were analysed in duplicate, and the cation content is given in Table I.

TABLE I.—*Daily Cation Content of the Low-salt Diet; Data Obtained by Analysis*

	Mean	Range
Sodium	15 mEq	11–23 mEq
Potassium	48 „	41–65 „
Calcium	631 mg.	614–654 mg.
Magnesium	312 „	305–344 „
Iron	11 „	10–12·5 mg.

Metabolic balance studies for sodium and potassium were obtained on 12 patients during 42 three-day collection periods, and for calcium, magnesium, and iron on six patients. The diet and stools were homogenized and aliquots ashed at 550° C. in a muffle furnace. The methods of analysis were the standard techniques previously described from this laboratory (Spencer, 1950; Nabarro *et al.*, 1952); inorganic iron and calcium were determined by the methods described by Hawk *et al.* (1947). Frequent observations were made on the plasma electrolyte concentrations and on the patients' weights.

A sulphonated polystyrene cation-exchange resin was administered as a 3:1 mixture of the ammonium and potassium phases (katonium), except for four patients who were given hydrogen-phase resin ("zeo-karb 225 H") and four who received a mixed cation-anion exchanger 29% in the potassium phase ("carbo-resin"). The usual dose was 20 g. thrice daily suspended in a liquid vehicle, taken after meals. Treatment lasted from two to eight weeks, with an average of 3.6 weeks. A special watch was kept for clinical and chemical complications, and records were kept of the patients' complaints.

There can be no doubt about the successful treatment of oedema: there is a rapid loss of weight, a water diuresis, and the swelling is grossly diminished.

Our results have been classified on the following basis:

	Excellent	Moderate	Failure
Loss in weight	Over 14 lb. (6·4 kg.)	14–7 lb. (6·4–3·2 kg.)	0–7 lb. (0–3·2 kg.)
,, of oedema ..	++++	++	+→0
Excess urine volume over fluid intake (Total)	Over 7 litres	7–3 litres	<3 litres

Seven of the 39 patients had insufficient oedema to permit classification of their response in this way, and these are grouped in Table II as "not assessed." They are included in the series to give a true overall account of the patients and of the incidence of complications during treatment.

Whereas the effective treatment of oedema is obvious, the credit is easily allotted to one particular form of therapy when it should be given to a combination of several, or, more correctly, recognized as a spontaneous improvement independent of any. To reduce this error, all patients were observed during a preliminary period of at least three weeks' (average five weeks) treatment by rest in bed, a low-salt diet, and fluid restriction; digitalis and mercurial diuretics were given when indicated. Except for the diuretics, this basal treatment was continued during the administration of the cation-exchange resins, and the results obtained are not considered as an unaided response to resin therapy.

Results

The clinical results obtained in 39 patients during the administration of ion-exchange resins are summarized in Table II. In 34% of the patients there was an excellent response, with clearing of massive oedema. Considerable improvement was obtained in a further 21%, with loss of oedema and weight up to 14 lb. (6.4 kg.); but in 45% no definite benefit resulted. If the seven patients with minimal oedema are excluded, an excellent response or considerable improvement was obtained in 65%. The resins were most effective in type II nephritis in the absence of uraemia, and in chronic rheumatic heart disease without cardiac cirrhosis. Poor results were obtained in patients with very chronic or recurrent congestive cardiac failure, whether due to advanced disease of the coronary arteries or to rheumatic heart disease; in those with renal failure; and in oedematous patients with a plasma sodium below 130 mEq/l. after long-continued treatment by salt depletion. Three seriously ill patients died during treatment—the first from a large pulmonary embolus, the second and third from advanced coronary artery disease.

TABLE II.—*Clinical Response of 39 Patients to Ion-exchange Resins, Classified According to the Standards Given in the Text*

	Total	Clinical Response			
		Excellent	Moderate	Failure	Not Assessed
Heart disease:					
Rheumatic ..	8	3	3	2	0
Ischaemic ..	19	4	3	5	7
Cor pulmonale	3	1	1	1	0
Renal disease:					
Type II nephritis	7	4	0	3	0
Chronic ,,	2	1	1	0	0
Total ..	39	13	8	11	7

Patients' Complaints

The frequency and type of complaints induced by the ingestion of resins were similar to those reported by Klingensmith and Elkinton (1952), and are summarized in Table III. In 67% there was discomfort, mainly related to the gastro-intestinal tract, and in 11% this was severe enough to cause the treatment to be abandoned. In 10% the complaints were moderately severe but were relieved by adjustments to the regime; while in 46% symptoms were slight. Although only 33% of these patients were entirely free from symptoms, severe gastro-intestinal complaints such as stomatitis and vomiting were confined to four subjects who were given the 100% hydrogen-phase resin in the early stages of this investigation. Resin preparations which were more palatable soon became available; these could be taken by most patients over periods of several weeks. Despite these improvements, patients still objected to the large bulk of resin that was required for effective treatment.

TABLE III.—*Incidence of Complaints During Cation-exchange Therapy*

Incidence of Complaints				Severity	
Anorexia ..	12	Weakness ..	7	Nil	33%
Constipation ..	11	Paraesthesia	4	Mild ..	46%
Nausea ..	9	Sore mouth	4	Moderate ..	10%
Vomiting ..	4	Haematemesis	1	Severe ..	11%
Abdominal pain	6	Alopecia ..	1		
Diarrhoea ..	4				

Biochemical disorders frequently developed during treatment with cation-exchange resins, but were not often serious. A characteristic metabolic response to resin therapy is illustrated in Fig. 1, which summarizes the data obtained in the following patient.

Case 4.—A woman aged 44 had type II nephritis, with gross anasarca, ascites, and pleural effusions. B.P. 110/70; serum albumin, 1.8 g./100 ml.; plasma cholesterol, 710 mg./100 ml.; blood urea, 24 mg./100 ml., with a maximum urea clearance of 83% of normal; albuminuria 16 parts per 1,000 (1.6 g./100 ml.). There was no improvement during three weeks' treatment with rest in bed and a low-salt diet containing 15 mEq of sodium. The ingestion of 60 g. a day of a cation-exchange resin was followed by complete relief of the oedema in four weeks, a weight loss of 16 kg. and a negative sodium balance totalling 1,860 mEq. The bowels were opened twice daily by a laxative. The faecal excretion of sodium was the greatest obtained in this series of patients, but an increased renal loss of water and salt accounted for 67% of the negative sodium balance. The stool potassium increased from 8 to 96 mEq a day, and the patient developed a negative potassium balance, hypokalaemia, and a compensated hyperchloraemic acidosis. These were corrected by supplements of potassium citrate, 2 g. three times daily. As the oedema disappeared the albuminuria decreased from 16 parts to 1 part per 1,000, the serum albumin gradually rose from 1.8 to 4.8 g./100 ml., and the plasma cholesterol fell from 710 to 265 mg. per 100 ml. One year later the patient was free of oedema and in good health, with normal renal function and normal urine.

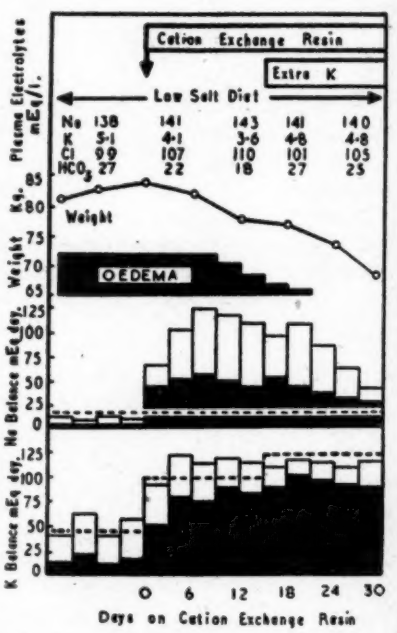

FIG. 1.—Metabolic balance chart of Case 4, type II nephritis, during treatment with ion-exchange resin. The black columns represent the stool electrolytes, while the renal excretion is unshaded. The intake is at the level of the interrupted lines, and the output is plotted upwards from zero. A negative balance is shown when the columns extend above the interrupted lines.

Sodium Depletion

The object of resin therapy was, of course, to deplete the body of excess sodium contained in the oedema fluid, and this was achieved in 8 out of 12 patients on whom balance studies were obtained (Table IV). The mean negative balance of sodium in these eight subjects was 48 mEq a day, and the total sodium depletion was very great in patients relieved of gross oedema. These studies demonstrate that the action of cation-exchange resins is not confined to the removal of dietary sodium as suggested by Dock and Frank (1950) and Danowski *et al.* (1951); but also show that they extract sodium from the body fluids, thus confirming the results of Duncan (1953). The faecal excretion of sodium varied greatly in different patients, and often declined during prolonged treatment, as it did in the studies of Cobbey *et al.* (1949), Emerson *et al.* (1951), and Barker and Mackay (1951).

TABLE IV.—*Sodium Balances of 12 Patients Receiving 60 g. of a Cation-exchange Resin and a Sodium Intake of 15 mEq a Day*

Case No.	Mean Daily Balance of Sodium			Total Balance			
	Urine Na (mEq)	Stools Na (mEq)	Balance mEq	Days	Sodium (mEq)	Water (Litres)	Weight (Kg.)
1	34	17	−36	18	−648	−10	−12
2	4	22	−11	14	−154	0	−1
3	36	21	−42	23	−966	−6	−7
4	18	64	−67	28	−1,876	−14	−16
5	0	12	+2	6	+12	0	0
6	37	41	−63	12	−766	−4	−6
7	2	21	−8	6	−48	0	−3
8	18	37	−40	10	−400	−1	−2
9	0	12	−3	6	−18	0	0
10	38	15	−39	28	−1,092	−9	−11
11	22	52	−57	6	−342	−3	−5
12	34	18	−37	35	−1,295	−9	−12

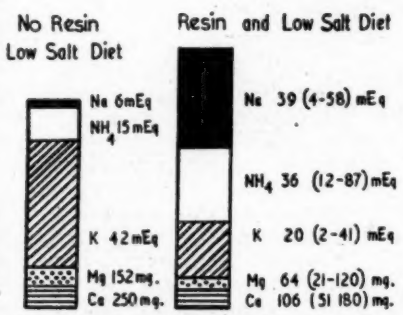

FIG. 2.—Mean daily excretion of cations in the urine of 12 oedematous patients before and during the administration of a cation-exchange resin and a low-salt diet.

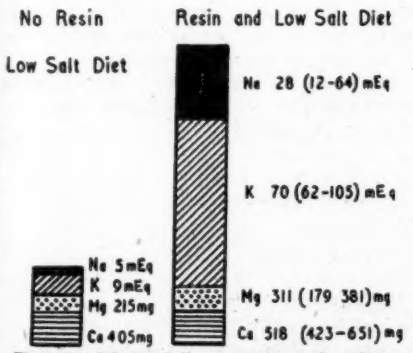

FIG. 3.—Mean daily excretion of cations in the stools of 12 oedematous patients before and during the administration of a cation-exchange resin and a low-salt diet.

A major factor, however, in the relief of oedema during resin therapy was an increased renal excretion of water and salt as noted by Greenman *et al.* (1951a). Thus the increment of sodium excretion generally had two components, an increased faecal excretion accounting for 42%, and that in the urine for the remaining 58% (Figs. 2 and 3).

The salt-depletion syndrome characterized by weakness, anorexia, nausea, muscular cramps, a fall in blood pressure, oliguria, and uraemia, together with a low plasma sodium, was not observed in any of our patients. In nine a complaint of anorexia and nausea was not associated with any other indication of salt depletion, and possibly resulted from the local action of the resin on the gastro-intestinal tract. Weakness was observed in seven subjects, but this was accompanied by a low plasma potassium. A normal blood urea and a plasma sodium over 130 mEq/l. is strong evidence against the existence of a serious degree of salt depletion. The plasma sodium concentration did not fall significantly in any of the patients (Fig. 4), the mean sodium concentration remaining unchanged at 137–138 mEq/l. (81 observations). These results are similar to those reported by Kraus (1950) and by Klingensmith and Elkinton (1952); but a fall in plasma sodium during resin therapy was observed by Greenman *et al.* (1953) and Weston *et al.* (1953). The initial plasma sodium concentration was usually lower in oedematous patients (mean, 137 mEq/l.) than in normal subjects (mean, 142 mEq/l.). In six it was below 130 mEq/l., but during administration of the ion-exchange resin it did not fall any lower. The blood urea did not rise during resin treatment except in those patients with pre-existing renal failure.

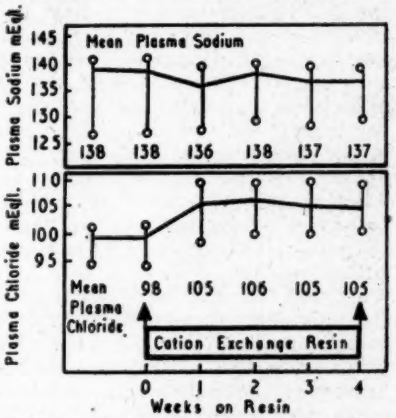

FIG. 4.—Plasma concentration of sodium and chloride ions before and during cation-exchange therapy. Means and ranges of 141 determinations on 28 patients. The graph is drawn through the means, while the vertical lines represent the ranges.

Potassium Depletion

Significant potassium depletion developed in 19 out of 39 patients, as shown by the incidence of muscular weakness (7), paraesthesiae (4), electrocardiographic changes (4), digitalis sensitization (4). The plasma potassium concentration fell below 4 mEq/l. in 26 out of 83 observations. Kraus (1950) and Greenman *et al.* (1953) experienced a comparable incidence. Potassium depletion results from a gross increase in the faecal excretion of potassium, mean 70 mEq a day (Fig. 3). The renal excretion of this ion usually decreased during resin therapy, except when potassium supplements were given (Fig. 2). The deficiency was closely related to the total intake of potassium, as it was less commonly found in patients taking a resin mixture 25% in the potassium phase, and was reduced still further by supplements of potassium citrate, 2 g. three times daily (Table V). Klingensmith and Elkinton (1952) avoided potassium depletion by administering resin 30% in the potassium phase, while Weston *et al.* (1953) recommended supplements of potassium salts for this purpose. Potassium depletion was not always avoided by these means, and occurred whenever our patients failed, through lack of appetite, to eat all their diet.

TABLE V.—*Effect of Potassium Intake on the Plasma Concentration and Balance of Potassium of Patients Taking 60 g. a Day of a Cation-exchange Resin*

Total Potassium Intake (mEq/day)	Potassium Balance (mEq/week)	Plasma Potassium After 2 Weeks
41–65 (diet + 100% hydrogen-phase resin)	−270	2·1–2·9 mEq/l.
70–98 (diet + 25% potassium-phase resin)	−80	3·2–5·1 „
90–108 (diet + 25% potassium-phase resin + 20 m.mols potassium citrate)	+20	4·3–7·5 „

Potassium Retention

Potassium retention occurred in two oedematous patients with impaired renal function during treatment with 25% potassium-phase resin, the plasma concentration rising to 7.5 and 7.8 mEq/l. This has also been described by Peel and Semple (1953).

Depletion of Calcium, Magnesium, and Iron

There was no clinical evidence of depletion of calcium, although tetany (Dock and Frank, 1950; Martz *et al.*, 1952), and a low serum calcium (Greenblatt and Gilwood, 1948; Greenman *et al.*, 1953) have been reported during prolonged treatment with ion-exchange resins. The mean faecal calcium excretion increased from 405 to 518 mg. a day, but renal losses decreased from an average of 251 to 106 mg. a day (Figs. 2 and 3), and a small negative balance was found in only two patients. The mean faecal excretion of magnesium rose from 215 to 311 mg. a day and renal losses fell from 152 to 64 mg. a day, producing a mean negative balance of 46 mg. a day. No changes were observed in the serum calcium, but in five subjects the plasma magnesium was low, the mean being 2.4 mg./100 ml. (normal 4 mg./100 ml.). The faecal excretion of iron was not altered by resin therapy, and the patients remained in balance. Apart from the experiments of McChesney *et al.* (1951) and McChesney (1952), little is known about the effects of resin therapy on the metabolism of magnesium and iron.

Acidosis

It was unusual for clinical signs of acidosis to appear during treatment with cation-exchange resins. The plasma chloride usually rose, the mean increasing from 98 to 105 mEq/l. (Fig. 4). This hyperchloraemia was associated with a decrease in the plasma bicarbonate, the mean falling from 25 to 16 mEq/l. (Fig. 5). These changes were more apparent when a hydrogen-cycle resin was used. Similar observations were made by Elkinton *et al.* (1952).

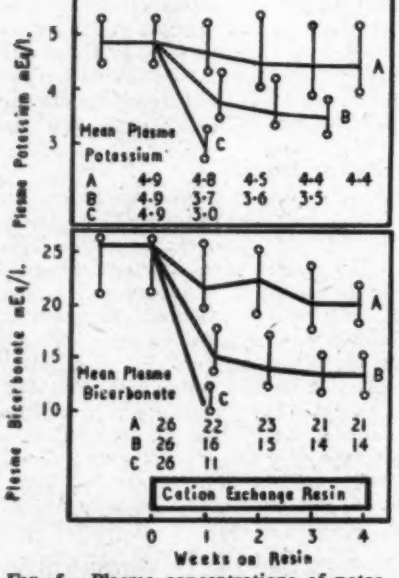

FIG. 5.—Plasma concentrations of potassium and bicarbonate ions before and during cation-exchange therapy. Means and ranges of 146 determinations on 28 patients. The graphs are drawn through the means while the vertical lines represent the ranges. A=Patients taking 60 g. of a 3:1 NH_4:K-phase resin and a dietary intake of 68 mEq K. B=Patients taking 60 g. of a 3:1 NH_4 K-phase resin and a dietary intake of 48 mEq K. C=Patients taking 60 g. of a 100% H-phase resin and a dietary intake of 48 mEq K.

With normal renal function, the decreased availability of potassium for the excretion of chloride and other anions was accompanied by the formation of an acid urine, and by a variable increment in the production of ammonium ion by the kidney. (Fig. 2). This compensation was deficient in early renal failure, and six patients developed clinical signs of acidosis, with the plasma chloride rising to 115 mEq/l. and the bicarbonate falling to 8 mEq/l. Acidosis was less apparent in four patients with renal disease who were treated with a mixed anion-cation exchanger, the mean plasma chloride being 106 mEq/l., and the bicarbonate 18 mEq/l.

Renal Failure

There was no evidence that renal failure ever resulted from resin therapy, but uraemia, acidosis, and electrolyte disorders were usually increased by this treatment. Serial determinations of the blood urea were made in 21 patients, and in 15 these were normal throughout. Six subjects had a raised blood urea before treatment; in one of these the blood urea fell, but in the other five it increased rapidly, and treatment by exchange resins was abandoned on this account.

Factors Relating to the Effectiveness of Exchange Resins

The efficiency with which cation-exchange resins increase the loss of sodium in the stools when the diet is constant appears to be related to the intestinal motility, to the body sodium content, and to the total intake of potassium in relation to the dose of resin.

Intestinal Motility.—On the same intake of sodium and resin the faecal excretion of sodium varied greatly from one patient to another (12 to 64 mEq a day, Table IV), but when measured over a period of several days was relatively constant for the same individual. In only 4 of 12 patients taking resins did the stool sodium (mean, 48 mEq a day) clearly exceed the intake, and these had loose motions; whereas in eight constipated patients the mean daily faecal excretion of sodium was 17 mEq a day. Laxatives consistently increased the loss of sodium in the stool, in part because of the extra quantity of resin passed and of the electrolytes contained in the larger volume of stool water, but largely due to the increment in sodium bound per gramme of resin. Potassium excretion also rose, but to a smaller degree, and the ratio of Na/K ions on the resin was greatly increased whenever the bowel motility was rapid. The stool sodium of four subjects taking resins was constantly very low, and, although this was increased by laxatives, the absolute loss of sodium was still comparatively small. The significance of these observations in relation to the dynamics of cation-exchange resins in the intestines is considered in detail by Spencer, Ross, and Lloyd-Thomas (p. 603 of this issue).

Total Body Sodium.—During prolonged treatment the mean faecal excretion of sodium declined from 38 mEq a day during the first week to 22 mEq a day after six to eight weeks, but at the same time the oedema became less extensive. Stool sodium was also greater in the first week of treatment in grossly oedematous patients (mean 46 mEq a day) than in those with slight oedema (mean 27 mEq a day). However, in four patients with extensive oedema associated with a plasma sodium between 126 and 130 mEq/l. the faecal excretion of sodium in response to resins was only 14 mEq a day. The ion-exchange resins are therefore more efficient when the total body sodium is increased, except when the plasma sodium concentration is low.

Dietary Potassium—The faecal excretion of sodium was decreased by increasing the dietary intake of potassium. With a combined potassium intake in the diet and on the resin of 88 mEq a day the mean excretion of sodium in a group of eight patients was 32 mEq a day. When extra potassium was given to a total of 108 mEq a day, the mean stool sodium declined to 24 mEq a day.

Discussion

The value of ion-exchange resins in the treatment of oedema is seriously limited by their small exchange capacity, and even more by the complete lack of specificity for the sodium ion. For example, the resin mainly used in the present study has a maximum capacity of only 3.1 mEq/g. and combines with three to four times as much potassium as sodium when in equilibrium with solutions containing equal proportions of these ions. Whereas resins are available with an *in vitro* capacity of up to 10 mEq/g. (Duncan, 1953), this has not been achieved at the hydrion concentration of the intestines. Moreover, all these resins exhibit a descending order of affinities for cations, $Ca^{++}>Mg^{++}>K^{+}>Na^{+}>NH^{+}>H^{+}$ (Nachod, 1949).

Considering the high concentration of sodium in the small-intestinal juices, the failure of cation-exchange resins to extract large amounts of this ion from the alimentary

tract of all subjects ingesting the resin has occasioned surprise (Dock and Frank, 1950). This has led to statements that ingested exchange resins extract sodium only from the diet and the upper small intestine (Hegsted *et al.*, 1951), or that increased secretory activity of the adrenal cortex in response to sodium depletion grossly alters the sodium content of the alimentary secretions (Berger *et al.*, 1951 ; Berger and Steele, 1952). Such conceptions of the action of exchange resins in the body are at variance with their known physical properties. Moreover, studies from this department, using the radioactive tracers Na^{24} and K^{42} have demonstrated that cation-exchange resins establish a dynamic equilibrium with the intestinal contents throughout the alimentary tract. There is a continuous interchange of ions to and from the resin and the body pool of sodium and potassium, with a rate of turnover at least equal to the total body content of these electrolytes every 24 hours. Large quantities of sodium are taken up by the resin in the small intestine even when there is only a small excretion of this ion bound to the resin in the stools. Most of the sodium taken up in the small intestine is exchanged for potassium in the colon (Spencer, Ross, and Lloyd-Thomas, p. 603).

From these observations, it appears that the efficiency of ion-exchange resins in the treatment of oedema could be increased in at least three different ways : first, by avoiding constipation ; secondly, by developing resins which have a high exchange capacity and a special affinity for sodium ; thirdly, by influencing cation exchange across the mucosa of the small intestine and colon, as by the use of specific enzyme inhibitors.

In their present stage of development cation-exchange resins cannot be recommended for general use in the treatment of oedema. Most oedematous patients respond well to treatment by rest in bed, a low-salt diet, digitalis, and mercurial diuretics. These measures are generally so simple, effective, and safe that cation-exchange therapy is not likely to replace them. Some patients, however, remain oedematous despite vigorous treatment by these standard methods, and in others mercurial diuretics are contraindicated. It is in these patients that resin therapy finds its most useful application ; but not all of these benefit, and in others serious complications may occur. An attempt has been made to define these two groups from an analysis of the results obtained in the present series and from those previously published. It now seems possible to select patients and manage their treatment with ion-exchange resins so that the majority become free of oedema without the risk of grave metabolic disorders.

Indications

1. *Cardiovascular Disease.*— In the absence of contraindications, treatment by ion-exchange resins is advised : (*a*) in persistent congestive cardiac failure of all types when pitting oedema remains after two to three weeks' treatment by standard methods ; (*b*) when mercurial diuretics or digitalis are contraindicated because of sensitivity, toxicity, or failure to respond ; and (*c*) during the convalescence from heart failure to prevent the recurrence of oedema. A satisfactory response is less often obtained in the presence of extensive disease of the coronary arteries, chronic congestive heart failure with cirrhosis of the liver and ascites, and whenever intensive salt depletion by other means has failed to relieve oedema. Two points merit further consideration. When the routine treatment of oedema has failed, resin therapy should not be delayed. Prolonged immobilization in bed leads to a steady deterioration, and greatly increases the risk of venous thrombosis and pulmonary embolism. Although the relief of oedema is highly desirable, it does not necessarily indicate any considerable improvement in cardiac function. In fact, treatment by resins or by other methods of salt depletion often removes many of the cardinal signs of heart failure.

Hypertensive Disease.—The use of cation-exchange resins together with a low-salt diet has been advocated as a more practical alternative to the rice diet in the treatment of hypertension (Page, 1951 ; Gill and Duncan, 1952). However, six of our patients with a high blood pressure were treated in this way, and in only one was there an appreciable fall of blood pressure. The most useful application of resin therapy in hypertensive disease therefore seems to be in cardiac failure. Little information is available concerning the value of exchange resins in patients with cardiac asthma or with hypertensive encephalopathy.

Renal Disease.—An excellent response may be obtained in type II nephritis and in early diabetic nephrosclerosis, provided that the blood urea is not raised. Patients with chronic nephritis and oedema commonly have advanced renal failure and are made worse by resin therapy. Sodium-phase resins have been successfully used in the management of hyperkalaemia occurring in anuria (Merrill *et al.*, 1950 ; Bull, 1952).

Contraindications

Gastro-intestinal Disorders.—A poor appetite, nausea, and dyspepsia interfere with the continued ingestion of the resin or, by causing gross fluctuations in the dietary intake, precipitate potassium depletion. Anorexia and nausea are among the symptoms of sodium depletion, and are often indications for an estimation of the plasma sodium and the blood urea.

Renal Failure.—The absence of an effective renal compensation for electrolyte disorders should generally be an absolute contraindication to treatment by ion-exchange resins. Metabolic complications such as severe hyperchloraemic acidosis, potassium retention or depletion, and a rapid elevation of the blood urea are common ; whereas relief from oedema is seldom achieved. The ammonium-phase resins contribute significantly to the nitrogen intake, and the usual dose is equivalent to the ingestion of 5 g. of urea a day. This extra load on the kidney would, if not excreted, raise the blood urea by 100 mg. per 100 ml. in ten days.

Advanced Liver Disease.—Ammonium phase resins may precipitate coma from ammonia intoxication in patients with advanced liver disease (Phillips *et al.*, 1952 ; Gabuzda *et al.*, 1952). Since effective sodium depletion can be achieved only by resins in the ammonium or hydrogen phases, and as the latter are unpalatable and likely to cause oesophageal erosions, resin treatment should not be used when liver function is severely impaired. Some excellent responses have been reported, however, in patients with cirrhosis of the liver (Gabuzda *et al.*, 1952).

Cation Depletion.—If in patients with heart failure the plasma sodium is consistently below 130 mEq/l., the daily urine volume is less than 500 ml., or the blood urea is over 60 mg./100 ml., treatment with cation-exchange resins is contraindicated. Uncorrected potassium depletion should be an absolute bar to cation-exchange therapy. This most commonly results from an inadequate intake of food associated with disease or operations on the gastro-intestinal tract, diarrhoea, and the previous use of exchange resins

Management of Cation-exchange Treatment

The principles of management are these : to use exchange resins as an adjuvant to salt restriction, with digitalis, mercurial diuretics, and rest in bed when necessary ; and to avoid complications by the exclusion of unsuitable patients, close supervision of the potassium intake, and the early detection of biochemical disorders.

Chemical Control.—Before treatment is begun it is advisable to measure the blood urea and the plasma concentration of sodium, potassium, and bicarbonate ions. The plasma potassium should be measured at intervals of one week. The treatment of patients with renal failure is not recommended, but, should there be doubt about the renal function, resin therapy may be tried, provided that weekly estimations of the blood urea, plasma bicarbonate, and potassium concentrations are available. It is helpful to keep a record of the weight, degree of oedema, urine volume, and bowel action.

Diet.—There is abundant evidence that the ingestion of exchange resins allows little increase in the intake of sodium (Greenman *et al.*, 1951a; Greenman *et al.*, 1953), and at first this should not exceed 20 mEq a day (1 g. salt). To avoid potassium depletion the intake needs to be maintained at 75 mEq (3 g.) potassium a day, in addition to that on the resin. The low-salt diet may not contain this amount of potassium, and the addition of fresh fruit will then form an acceptable supplement of this ion. Since a constant and relatively high intake of potassium is the chief safeguard against potassium depletion, close supervision of the patients' meals is required. Any failure to eat the diet should be recorded by the nurse and reported to the physician in charge. The addition of 1 pint (570 ml.) of milk a day makes the diet more palatable, and helps to prevent depletion of calcium and magnesium during prolonged therapy. Although exchange resins absorb thiamine (Nachod, 1949; McChesney and McAuliff, 1950), no evidence of vitamin deficiency has been observed during treatment (Greenman *et al.*, 1953). Nevertheless it may be advisable to provide a compound vitamin supplement. In the treatment of type II nephritis the introduction of up to 150 g. of protein into the diet is made more effective by the administration of exchange resins, which take up the increment in sodium.

Selection and Administration of the Resin.—Of the available preparations those containing a 3 : 1 mixture of the ammonium and potassium phases of a sulphonic or carboxylic cation-exchange resin are most generally useful. Ammonium-phase resins are contraindicated in advanced liver disease (Phillips *et al.*, 1952). The resins now in common use in this country have an effective combining capacity of about 3 mEq/g., and in adults the effective dose is 45–75 g. a day. These preparations are pleasantly flavoured, making them easy to take as a suspension in water or in fruit juices. It is immaterial whether the resins are given before or after meals (Martz *et al.*, 1952). The intermittent use of resins has been advocated by Weston *et al.* (1953). This reduces the risk of potassium depletion, the resin being given on five days a week with intervals of two days, in which potassium citrate, 2 g. three times a day, is provided in a simple mixture. There may be little response in the first ten days of treatment, but some of these patients rapidly improve thereafter. Resin therapy should therefore not be abandoned for this reason in less than two to three weeks.

Domiciliary Treatment.—In selected patients, treatment with ion-exchange resins and a modified low-salt diet (2 g. salt) has been continued at home for many months. This has successfully prevented the reaccumulation of oedema, and in this way has reduced the frequency of readmissions to hospital. These patients attend the follow-up clinic at intervals of two to four weeks for clinical supervision and estimation of the plasma electrolytes and the blood urea. Voyles and Orgain (1951) and Aaron and Weston (1952) have reported their experience of long-continued resin therapy.

Care of the Bowels.—Many patients have become constipated during the administration of exchange resins, and this may give rise to abdominal swelling and discomfort (Arnold, 1951). In the present study it has been demonstrated that the efficiency with which resins remove sodium from the gastro-intestinal tract was decreased by constipation and increased by the use of aperients. For this reason it is recommended that the bowels should be opened once or twice a day, obtaining soft stools by any laxative which suits the patient. Salts should not be used for this purpose, and diarrhoea must be avoided.

Administration of Digitalis.—An increased incidence of digitalis toxicity has been reported during treatment with cation-exchange resins (Kraus, 1950; Weston *et al.*, 1953). Gross disturbances of this kind were seen in 3 out of 28 patients in this series who were taking maintenance doses (0.25 to 0.75 mg. a day) of digoxin (Fig. 6). These occurred when the plasma potassium was reduced, and were relieved by the administration of potassium citrate. Special care should therefore be taken to avoid potassium depletion in patients taking both digitalis and ion-exchange resins. The maintenance dose of digitalis may be halved when the resin is begun, and increased later as indicated. The relation between potassium metabolism and the action of digitalis on the heart has been reviewed by Enselberg *et al.* (1950) and Lown *et al.* (1951).

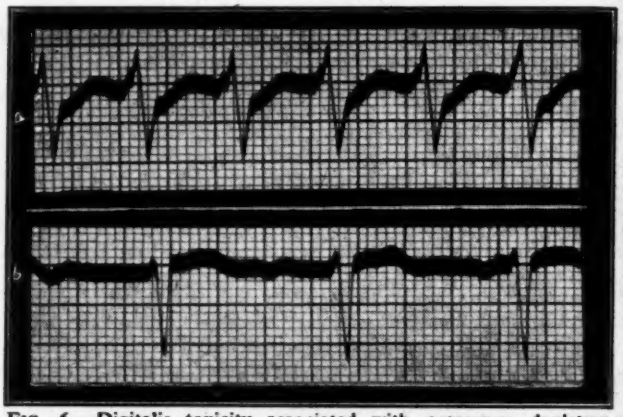

FIG. 6.—Digitalis toxicity associated with potassium depletion during the course of cation-exchange therapy. (*a*) Multiple ventricular extrasystoles. E.C.G. Lead I (rate 150 per minute). Plasma potassium, 3.6 mEq/l. (*b*) Auriculo-ventricular dissociation. E.C.G. Lead III (ventricular rate 79, auricular rate 130 per minute). Plasma potassium, 4.1 mEq/l.

Mercurial Diuretics.—Martz *et al.* (1952) and Elkinton *et al.* (1952) have reported that the efficiency of mercurial diuretics was increased during the administration of cation-exchange resins, and our recent experience confirms this observation.

Paracentesis.—When patients lose their oedema, effusions into the pleural and peritoneal cavities commonly persist. These are best removed by paracentesis in the early days of resin treatment.

Summary

Cation-exchange resins were administered to 39 patients with chronic oedema resulting from cardiac or renal disease.

A satisfactory response was obtained in 65% of those with gross oedema. Minor complaints induced by resin therapy occurred in 67%, but serious chemical disorders were uncommon.

Metabolic balance data were obtained in 12 patients, and the results are discussed and analysed in relation to the incidence of biochemical complications and to the clinical effectiveness of cation-exchange therapy.

Recommendations are made on the use of cation-exchange resins, with particular reference to the selection and management of patients and the methods by which dangerous complications can be avoided.

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CATION EXCHANGE IN THE GASTRO-INTESTINAL TRACT

BY

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Cation-exchange resins are surprisingly inefficient at removing sodium from the gastro-intestinal tract. It had been anticipated from *in vitro* studies (Morton, 1951) that the large preponderance of sodium over other cations in the fluids of the small intestine would more than compensate for the greater affinity which such resins exhibit for potassium. In practice, when cation-exchange resins are administered to patients on a low-salt diet they remove far more potassium than sodium (Dock and Frank, 1950; Barker and Mackay, 1951; Greenman *et al.*, 1951). It has been suggested, therefore, that exchange resins extract sodium only from the diet, their activity being confined to the upper small intestine (Hegsted *et al.*, 1951). This concept is opposed by McChesney (1952) and seems to be at variance with the physical and chemical properties of the resins.

Despite the abundance of clinical and experimental studies there appears to be little direct evidence concerning the action of ion-exchange resins at various levels in the intestinal tract. Data of this kind have been obtained in the present investigation. The rates of turnover of sodium and potassium ions to and from the exchange resin have also been measured with the radioactive tracers Na^{24} and K^{42}. From these results the activity of cation-exchange resin has been interpreted in terms of a constantly changing series of dynamic equilibria between the cations on the resin and those in the intestinal fluids. Through this medium all the cations in the body continually exchange with those on the resin. The activity of the exchange resin is not confined to one region of the intestinal tract. On the contrary, cation exchange is continuous throughout the length of the gut. The rates of turnover of cations to and from the resin are not constant, however, but undergo a regular sequence of change as the resin passes from the stomach onwards to the rectum. One result of this complex cycle of activity is that when cation-exchange resins are administered in the ammonium or hydrogen phase there is a predominant uptake of sodium in the small intestine. Most of this sodium is exchanged for potassium and other ions in the colon.

Materials and Methods

These have largely been described in the previous paper (Spencer and Lloyd-Thomas, p. 597 of this issue). The resin used in these studies was a sulphonated polystyrene of equivalence 3.1 mEq per g. of resin. The phase and mesh size is given separately in the accounts of the individual experiments.

The total electrolyte contents of the stools, intestinal contents, and enema samples were obtained by flame photometry of dilute solutions prepared from ashed aliquots of the entire specimen. The resin was isolated by flotation from aliquots of the homogenized intestinal fluid. This was facilitated by administering part or all of the resin as a coarse (40–80 mesh) powder. The resin so obtained was dried at 60° C and weighed. The cations were eluted with 4N HCl and estimated as before. The radioactivity of the acid extract was determined in a liquid counter.

Composition of Ion-exchange Resin in the Small and Large Intestines

Samples of fluid and exchange resin were obtained from the small intestine by Miller–Abbott tube (2), from a fresh ileostomy (7), and at post-mortem examination from three patients who had died suddenly from coronary thrombosis (2) or pulmonary embolism (1). In the necropsy studies samples were also taken from the proximal colon and rectum. The subjects had all been taking a low-salt diet and a cation - exchange resin, as previously described by Spencer and Lloyd-Thomas at p. 597. Their plasma sodium concentrations were in the range 137–141 mEq per litre.

SITE	SMALL INTESTINE RESIN	PROXIMAL COLON RESIN	DISTAL COLON RESIN
No. Obs.	11	3	15
Na mEq/g.	1·4	0·9	0·4
K "	0·5	0·8	1·1
Na:K	2·8	1·1	0·36

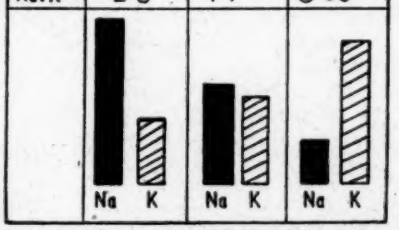

FIG. 1.—Mean concentration and relative proportions of sodium and potassium ions bound to a cation-exchange resin at different levels of the human gastro-intestinal tract.

Results.—Resin taken from the small intestine had a similar composition in all the subjects. The results of these analyses, together with those for the resin from the colon, are summarized in Fig. 1. From these data it was apparent that the exchange resin had taken up large amounts of sodium in the small intestine even though the patients were on a low-salt diet. In the distal part of the colon there was more potassium bound to the resin than sodium, while

in the proximal colon the composition of the resin was intermediate between these two. These results suggested that most of the sodium ions taken up by the resin in the small intestine were exchanged for potassium in the colon. A study was therefore made of the transfer of ions between the mucosa of the colon and the cation exchange resin.

Observations on Cation-exchange Resin in the Colon

Three experiments were completed on patients taking a low-salt diet, without exchange resin by mouth. The colon was washed out with water. Two hours later approximately 5 g. of a 40–80 mesh sulphonic acid cation-exchange resin 100% in the sodium phase was introduced into the bowel through a high rectal tube. The foot of the bed was raised, and at intervals of 60–120 minutes samples of resin were removed via the tube or were obtained as the bowels were opened. In one group of experiments the sodium-phase resin was labelled with Na^{24}, and in another $K^{42}Cl$ was injected intravenously two hours before the enema was given.

Results.—The composition of the exchange resin as put into the lower bowel and as removed 60–120 minutes later is given in Table I. Although samples of resin removed

TABLE I

Cation	In (mEq/g. of Resin)	Out (mEq/g. of Resin)	
		Mean	Range
Na ..	2·8–3·1	1·4	2·5–0·8
K ..	0	1·1	1·9–0·3
Ca ..	0	0·14	0·21–0·06
Mg ..	0	0·18	0·24–0·08

from the colon varied in composition the results were qualitatively similar. The exchange resin regularly lost sodium in the colon, and this was replaced by potassium and to a smaller extent by calcium and magnesium. The duration of these experiments was comparatively brief, and the results of these analyses do not represent the ultimate distribution of cations on the exchange resin. The net rates of exchange as measured by the radioactive isotopes were similar to those found by chemical analysis. It was impracticable to obtain frequent samples of resin from the colon, and for this reason it was not possible to compute the rates of ion exchange both to and from the resin. Data of this kind were therefore obtained by experiments on rats.

Effect of Laxatives

It had previously been observed that, of patients taking a low-salt diet and a cation-exchange resin, those with loose motions lost more sodium in the stools than did the subjects who were constipated (Spencer and Lloyd-Thomas, p. 597). From seven patients who were constipated on such a regime the stools were collected and analysed before, during, and after a period of 48 hours in which the motions were kept fluid by the administration of castor oil or cascara.

Results.—The effect of laxatives was to increase the mean faecal excretion of sodium from 21 to 63 mEq a day, and that of potassium from 69 to 103 mEq a day, as shown in Table II. It was apparent that the faecal excretion of sodium

TABLE II.—*Daily Excretion of Cations in the Stools*

	Total (mEq)		Bound to Resin (mEq/g.)		
	Na	K	Na	K	Na/K
Resin only ..	21 (13–37)	69 (58–106)	0·32	1·2	0·26
Resin and purge	63 (39–114)	103 (73–127)	0·68	0·93	0·73

had increased for three different reasons: first, the greater quantity of stool and resin passed; secondly, the electrolytes in the extra volume of stool water; and, lastly, because of the increment in sodium bound to each gramme of resin. The method of analysis permitted the separation of these components. When the bowels were freely open the mean excretion of sodium bound to resin increased from 0.32 to 0.68 mEq/g. and the Na/K ratio rose from 0.26 to 0.73. It was thought that laxatives had modified the uptake of cations on the resin by changing the composition of the intestinal fluids and by accelerating the passage of exchange resin from the small intestine through the colon into the stools.

Experiments with Isolated Loops of Rat Intestine

Methods.—Loops of small intestine and colon of 250-g. rats were isolated by ligature, under ether anaesthesia. Special care was taken to preserve the blood supply. Small quantities of a 40–80 mesh carboxylic cation-exchange resin were introduced into the loops with the minimum amount of water, and the loops were then returned to the abdomen. At timed intervals (20–30 minutes) 2-cm. lengths of gut were excised and their content of resin recovered and analysed as described above. In one group of rats, $Na^{24}Cl$ or $K^{42}Cl$ (1 μc. in 1 ml. of isotonic carrier) was injected subcutaneously two hours before the resin (100% hydrogen phase) was introduced into the gut. The data obtained permitted the calculation of the rates of transfer of sodium or potassium from the body fluids to the resin. In a second group, resin labelled with Na^{24} or K^{42} was introduced into the gut so that the rates of exchange in the direction resin to body fluid could be calculated. In a third group, resin which had equilibrated with the contents of the small intestine was transferred to the large intestine and samples of resin were removed at intervals and analysed as before. The analysis and interpretation of the data obtained follows the methods developed by Visscher *et al.* (1944) in their studies of cation transport across the intestinal mucosa. Details of these experiments will be reported elsewhere.

Results.—There is a continuous transfer of cations on and off the resin. The change in concentration of cations on the resin over a period of time is merely the net rate of transport, which is the algebraic sum of the rates of transport of cations on and off the resin. The net uptake of sodium and potassium by resin in the gut is shown in Fig. 2.

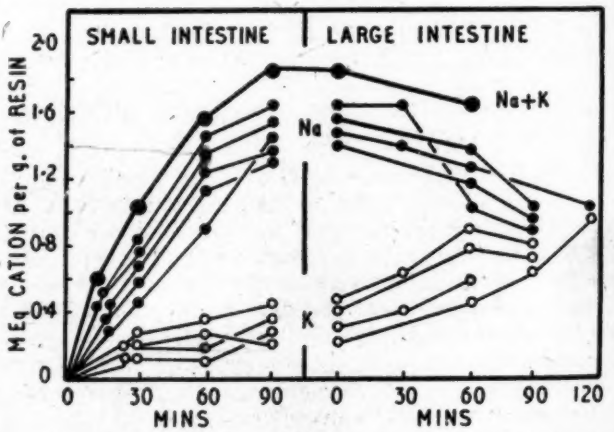

FIG. 2.—Net uptake of sodium potassium by a cation-exchange resin in the small and large intestine of the rat.

In the small intestine, 1 g. of resin took up 1.2–1.5 mEq of sodium and 0.3–0.45 mEq of potassium. When the resin in this state was transferred from the small to the large intestine it gradually lost sodium ions, but continued to take up potassium. The total Na^+ and K^+ bound to the resin fell, owing to the uptake of Mg^{++} and Ca^{++}. The ratio of sodium to potassium was 3–4:1 in the small intestine, 1:1 in the large intestine, and 0.4:1 in the faeces. The rates at which sodium and potassium were exchanged in the small intestine between the resin and its surrounding fluid after the attainment of a dynamic equilibrium were also determined. From these results it was calculated that all the sodium on the resin was turned over once every 60–75 minutes. With 5 g. of resin in the rat's small intestine, the turnover of sodium ions to and from the resin would

approximately equal the exchangeable body sodium every two hours. The turnover rate of potassium was one-half to one-third that of sodium.

Discussion

When a cation exchange resin is shaken up with an electrolyte solution in a simple container, such as a test-tube, an equilibrium distribution of ions between the resin and the solution is quickly reached. In the present experiments more than 90 minutes was required before a steady state was reached between the resin and the fluid in the rat's small intestine. The presence of resin in the gut introduces, in effect, a further electrolyte-containing compartment into the organism, the sodium and potassium of which require time to come into equilibrium with the exchangeable sodium and potassium of the body.

Even when the concentration of cations on the resin has reached the maximum for that section of the intestinal tract, there is a constant exchange of ions to and from the resin and the surrounding fluid. A series of dynamic equilibria are established between the cations on the exchange resin, those in the intestinal fluids, and eventually with those in the total exchangeable pool of cations in the body. In the rat the total exchange of sodium to and from the resin in two hours was found to be approximately equal to the entire sodium content of the body. The turnover rate for sodium was about three times greater than that for potassium. Exchange rates in the colon were slower and more variable than those in the small intestine.

However, the final concentration of cations on the exchange resin in the gut appears to depend only on the type of resin, the *p*H, and the concentration and physical properties of the different ions in the surrounding fluid. When an exchange resin was placed in solutions of the same *p*H and electrolyte concentration as the fluids of the small intestine and the colon, it took up cations in approximately the same proportions as those found on resin actually removed from these sections of the intestinal tract.

As the cation-exchange resin passes along the intestinal tract it undergoes a sequence of changes (Fig. 3). These net changes in the concentration of ions on the resin are the resultant of the simultaneous movement of cations on and off the resin.

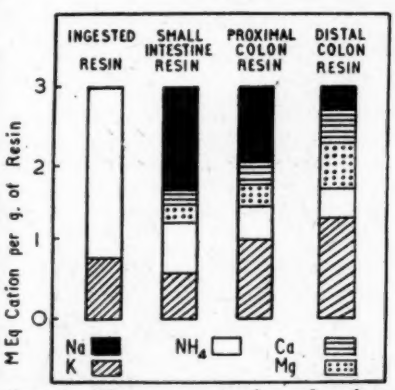

FIG. 3.—Mean concentration of cations bound to an exchange resin during its passage along the human gastro-intestinal tract.

In the fasting stomach, at a *p*H of 2 or less, the resin remains largely in the hydrogen phase. If ingested in the ammonium and potassium forms some of these ions are exchanged for hydrogen ions. When there is a simultaneous ingestion of exchange resin and food, the net uptake of cations by the resin will vary greatly according to the electrolyte content of the diet and the *p*H of the stomach. The hydrogen-ion concentration is important for two reasons. First, the uptake of cations by carboxylic resins, and to a much smaller extent by sulphonic acid resins, is dependent on the *p*H (Nachod, 1949). Secondly, in the presence of phosphate ions the availability of calcium and magnesium ions for exchange is greatly increased in acid solutions. Under these conditions there is a considerable uptake of calcium and magnesium from the diet of an acid stomach (*p*H 3–6). Because of the great affinity of exchange resins for these ions, they are not subsequently displaced to any considerable extent by sodium or potassium ions.

In the small intestine there is a net uptake of sodium reaching up to 1.5 mEq/g. of resin in our experiments, and of potassium 0.3–0.5 mEq/g. of resin. Here the concentration of sodium in the intestinal fluid (86–134 mEq/l.) is much greater than that of potassium (6–17 mEq/l.), and this more than compensates for the smaller affinity of the resin for sodium as compared with potassium. If the ingested resin contains more potassium than 0.5 mEq/g. of resin the excess is exchanged for sodium. The concentration of electrolytes in the jejunal fluids is altered by ingested food, and this factor influences the net uptake of cations by the resin at this level of the intestinal tract. With a low-sodium, high-potassium diet, the resin takes up a preponderance of potassium ions in the jejunum, most of which is displaced by sodium lower down in the small intestine. Resin ingested in the ammonium phase continues to lose this ion.

By the time the resin has reached the proximal colon a net loss of sodium is already apparent, largely in exchange for potassium ions. This process continues as the resin passes along the colon to the rectum, the concentration of cations on the resin in the proximal colon being 0.9 mEq of sodium per g. of resin, and 0.8 mEq of potassium per g. of resin: and in the stools 0.4 mEq of sodium and 1.1 mEq of potassium per g. of resin. The concentration of electrolytes, expressed as mEq/l. of water of the gut contents, gradually changes along the course of the large intestine. In the caecum the values were similar to those in the small intestine—sodium 93–118 mEq/l., potassium 12–21 mEq/l. In the sigmoid colon and in the stool water, however, there was generally more potassium than sodium, the concentrations being sodium 6–38 mEq/l., potassium 14–44 mEq/l. Throughout the length of the gut the cations in the intestinal fluids compete for the free valencies in the resin. In the colon the net exchange of sodium ions bound to the resin for potassium and other ions merely results from the change in concentration and relative proportions of these ions in the fluids of the large bowel. It is possible that this exchange of sodium for potassium may begin in the distal part of the small intestine. When resin is ingested in the ammonium phase some 10–20% of the resin in the stools is still in this phase. The low-salt diet used in these studies was also comparatively low in calcium and magnesium, but resin in the stool contained up to 0.3 mEq/g. of resin of both these ions, the quantity actually bound to the resin varying with the *p*H of the stools when analysed.

When dietary sodium is low there is a reduction in the excretion of sodium bound to exchange resin in the stool (Dock and Frank, 1950; Greenman *et al.*, 1951; Martz *et al.*, 1952), and this decrease is most conspicuous in salt-depleted subjects (Emerson *et al.*, 1951). Berger and Steele (1952) have suggested, therefore, that the electrolyte content of the intestinal fluids is altered by salt depletion, in response to increased secretory activity of the adrenal cortex. The observation that injections of deoxycortone acetate decrease the faecal excretion of sodium bound to resin (Berger *et al.*, 1951) appears to support this concept. While it is true that McCance (1938) has reported change in the electrolyte content of the salivary and gastric juices during severe salt depletion, there does not appear to be any direct evidence of similar alterations in the composition of the fluids in the small and large intestines.

In the present studies the patients were maintained on a low-salt diet, but were not seriously depleted of sodium. Under these conditions, exchange resin removed from the small intestine was still predominantly bound to sodium. Salt restriction did not materially alter the sodium content of the fluid in the small intestine. In the same patients the excretion of sodium bound to resin in the stool was low. It would therefore seem that the effect of salt restriction was to make the colon more efficient at removing sodium from the resin. The reabsorption of sodium is a normal function of the colon, and the increased efficiency of this mechanism during salt restriction is comparable to that exhibited by the sweat glands and the kidneys.

By the use of laxatives it was possible to increase the faecal excretion of sodium during the ingestion of cation-exchange resins. However, a great increment in sodium excretion was obtained only when the stools were kept fluid. Vigorous treatment of this kind is not recommended, as, besides the discomfort, purgatives greatly augment the excretion of potassium in the stool water. During treatment with cation-exchange resins the aim should be to keep the motions loose but not actually fluid, and to supplement the dietary intake of potassium. Saline laxatives, the cations of which become bound to the resin, and liquid paraffin, which coats the resin with a water-repellent film, must of course be avoided.

Summary

The net uptake of cations by an exchange resin was determined at different levels of the intestinal tract in man. The rates of turnover of Na^{24} and K^{42} to and from the resin were also measured in the small and large intestines of the rat.

A series of dynamic equilibria are established between the cations on the exchange resin and those in the intestinal fluids. These transfers are continuous throughout the gut, but the rates of turnover and the net uptake of cations by the resin change as it passes onwards from the stomach to the rectum.

Cations throughout the body continually exchange with those on the resin by way of the intestinal fluids.

These concepts have been used to interpret the results obtained during the treatment of patients with cation-exchange resins.

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The Minister of Food, Major Gwilym Lloyd-George, M.P., has approved for publication a report presented to the Food Standards Committee by its Metallic Contamination Subcommittee on the amount of zinc that should be permitted in food. The report recommends that no exception need be taken to the presence of traces of zinc in foods in amounts not exceeding, in "beverages ready to drink," 5 parts per million (p.p.m.), and in other foods 50 p.p.m. This recommendation is subject to a few exceptions; thus a limit of 100 p.p.m. has already been prescribed for edible gelatin, and the subcommittee sees no objection to the sale of certain animal and vegetable products with a high natural zinc content—even when it exceeds 50 p.p.m. Attention is drawn in the report to the undesirability of using zinc and galvanized iron containers in the preparation or storage of foods. The subcommittee states that zinc, like copper, has a definite physiological function in the human organism. The normal daily intake of an adult is estimated at 12 mg. It considers that public health requirements would be met by observance of the limits proposed, and that, in the absence of any new developments, statutory effect need not be given to the limits recommended.

CARCINOMA COMPLICATED BY PROXIMAL MOTOR NEUROPATHY DUE TO VITAMIN-B DEFICIENCY

BY

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Though the number of cases of neuropathy associated with cancer is not so far very great, it is probable that many are overlooked, and that patients who might otherwise have lived useful lives for months or years suffer unnecessarily or come to an untimely end. The general practitioner must usually undertake the care of the patient with incurable malignant disease, and he is unlikely to be aware of this particular complication, still less that it responds well to the correct treatment if given promptly.

The Literature

Spillane (1947) reviewed the effects on the central nervous system of deficiencies of the various members of the vitamin-B group. Cases of neuropathy associated with carcinoma, including many cases of true peripheral neuropathy with sensory disturbances, are reviewed by Denny-Brown (1948) and by Lennox and Prichard (1950). The cases of true peripheral neuropathy are not dealt with here.

Five cases of neuropathy associated with carcinoma of the bronchus were reported by Lennox and Prichard. Two actually under their care (Cases 1 and 2) were typical of peripheral neuropathy with motor and sensory phenomena. The other three (Cases 3, 4, and 5) seem quite different, and may have been similar to the cases reported below from the Royal Cancer Hospital. The points of difference which stand out include:

Cases 1 and 2	*Cases 3, 4, and 5*
1. Sensory symptoms early.	1. Absent or minimal sensory phenomena, subjective and objective.
2. True peripheral weakness—for example, foot-drop.	2. An early symptom, at any rate in Cases 3 and 5, was inability to sit up in bed; perusal of the clinical description leaves a very real doubt regarding the main sites of weakness. The evidence suggests that the proximal musculature bore the main brunt. In Case 4 the details given are insufficient to throw light on this aspect.
3. Chronic course and absence of brain-stem lesions.	3. Palatal weakness, dysphagia, and, in Case 5, facial weakness were involved—that is, the brain-stem was rapidly and severely affected.

Heathfield and Aldren-Turner (1952) described a case of neuropathy associated with presumed carcinoma of the bronchus. In this case no sensory symptoms and few sensory signs were elicited, and the weakness seems to have involved the hips and knees as well as the ankles and, only slightly, the

grip. Here, therefore, the proximal muscles were involved significantly. It is of note that a pyruvate-tolerance test done before treatment was abnormal, and returned to normal later. The sensory abnormalities and the peripheral element of the weakness responded to aneurine, nicotinic acid, and riboflavine therapy, though some weakness, especially of the hips, remained. No pantothenic acid or pyridoxine was used.

It is worth recalling that Spies *et al.* (1940) reported that patients who recovered from pellagra after treatment which did not include pyridoxine were significantly helped by the intravenous administration of this substance; the symptoms relieved included muscular weakness and difficulty in walking.

Experimental Work

With regard to experimental work on animals, Follis and Wintrobe (1945) reported peripheral nerve lesions without posterior root ganglion damage in pigs deficient in pyridoxine. With pantothenic acid deficiency, however, the posterior root ganglia were early affected. An interesting description is given of the gait of pigs affected. With pyridoxine deficiency "a swaying of the hindquarters and twisting of the legs with a broad base" was seen, but with pantothenic acid deficiency "a jerky military goose-step" with no twisting was observed. Follis and Wintrobe failed to produce nerve lesions with aneurine deficiency alone.

Swank and Adams (1948) confirm the above to a large extent, particularly the twisting movements of the hind legs, and later the forelegs, with pyridoxine deficiency, and the stiff "goose-step" gait with pantothenic acid deficiency. They also demonstrated with rough tests the preservation of sensation in pyridoxine deficiency, at any rate in the early stages. The final pictures of both deficiencies when prolonged are reported to be similar.

This peculiar swaying gait of the pigs I would interpret as due to weakness of the proximal musculature and comparable with the trick movements noticed so often in true myopathies. The "military goose-step" is presumably due to peripheral weakness with, possibly, tenderness and paraesthesiae contributing; but other explanations are equally plausible and cannot be excluded.

Meiklejohn (1940) and Wintrobe *et al.* (1944) reviewed the evidence on the part played by aneurine in neuritis, and concluded, in brief, that its deficiency was not the cause. Swank and Adams reviewed the evidence again, and concluded that aneurine did have an antineuritic property. This point seems to be far from settled, and further experimental work will be needed before a definite decision can be made. Similar doubts exist about the role of nicotinic acid and riboflavine in the pathology of neuritis.

Two Distinct Types

There does not appear to be any previous record which distinguishes two distinct types of neuropathy associated with cancer—one primarily affecting the proximal musculature and the other primarily peripheral and associated with sensory disturbances. An account is given of two cases of the former seen at the Royal Cancer Hospital.

Case 1

A painter aged 61 had had pain in the left side of the face for seven months before admission, and for six weeks had noticed swelling of the left cheek and a discharge from the left nostril. Ten days previously an *x*-ray examination at the Royal National Throat, Nose, and Ear Hospital had revealed destruction of the bony walls of the left antrum, and a fenestration of the palate had been performed by Mr. Maxwell Ellis. A biopsy taken then was reported by Dr. J. W. Whittick as showing very active, poorly keratinizing squamous-cell carcinoma. The patient had noticed weakness, of fairly sudden onset, particularly of the spine and arms, about a week before admission to hospital, and had developed oedema of the arms and a rash. Prior to this the only neurological symptoms were those attributable to pressure of the growth on the floor of the orbit—namely, slight proptosis of the left eye with diplopia; numbness to pinprick and cotton-wool of the first and second divisions of the left fifth nerve but sparing the upper branches of the first division which supply the scalp and forehead; and diminution of the left corneal reflex. A slightly lower motor neurone weakness of the left facial nerve affecting the mouth may also have been due to local involvement.

Examination on the fifth day showed gross weakness of the axial spinal muscles, including the sternomastoids, trapezius, pectoral girdle, and ilio-psoas muscles, but little or no weakness of grip, or dorsiflexion of the ankle or other peripheral muscles. The patient was unable to sit up in bed, to hold his arms horizontally in front of him, or to raise a leg off the bed unaided; only with difficulty could he lift his head off the pillow. No sensory changes could be detected, except those mentioned above in the first two divisions of the left fifth nerve. There was no significant wasting, and the reflexes were present in the right arm but not in the left. The knee-jerks were diminished, the ankle-jerks brisk, and the plantars flexor. There was slight oedema of both arms, the left more than the right; at the time this was attributed to drooping of the shoulders leading to compression of the venous return from the arms. Undoubtedly this was part of the truth.

The skin eruption was described by Dr. H. W. Gordon as "curious telangiectatic papular areas on the back of the neck behind the ears, on the sides of the neck, on the outer side of the left arm, and on the right side of the face, which appeared about two weeks before admission. I am at a loss for an exact diagnosis." It was also noticed that there was a mucopurulent conjunctivitis of the left eye, which recovered with routine treatment.

On the third day his serum globulin was 3.12 g.%, albumin 3.25 g.% (total protein 6.37 g.%), and an *x*-ray film of the chest showed a normal heart shadow. On the sixth day R.B.C. were 4,520,000; Hb, 77%; W.B.C., 19,000. The day after this a Caldwell–Luc operation was performed by Mr. W. A. Mill, and a swab of the pus obtained at that time showed a profuse growth of coagulase-positive *Staphylococcus aureus*, insensitive to penicillin. On the seventh day a lumbar puncture produced a clear C.S.F. under normal pressure. There was no block, and the total protein was 15.2 mg. per 100 ml., there was no increase in the cell count, and the Lange and Wassermann reactions were negative. Up to this time his weakness and oedema had increased, but there was no other change. He had a temperature each night of 99° F. (37.2° C.) for the first ten weeks, after which it subsided.

He had been receiving, in addition to his food, 5,000 units of vitamin A, 30 mg. of vitamin C, 600 units of vitamin D, 1 mg. of aneurine, 1 mg. of riboflavine, and 15 mg. of nicotinic acid daily, with some ferrous sulphate, this being a routine at the Royal Cancer Hospital. On the 20th day this was supplemented by "becozym" injections, providing in all 11 mg. of aneurine, 5 mg. of riboflavine, 55 mg. of nicotinamide, 4 mg. of pyridoxine, and 6 mg. of pantothenol daily.

From the 21st day a remarkable change began—namely, his weakness rapidly decreased so that he was able to hold up his arms and almost sit upright unaided. The oedema, however, increased and involved the legs, and did not begin to improve until about the 36th day, certainly not earlier. On the 30th day the dose of aneurine was raised to 111 mg. daily, and given intravenously. Owing to a misunderstanding it was omitted on the 31st to 33rd days inclusive, but was continued thereafter until the 39th day. By the 37th day his recovery of power was complete, and he gave a demonstration of shadow boxing in mistaken enthusiasm, before being promptly confined to bed again, as he still had an increased venous pressure and oedema. A brisk diuresis occurred between the 39th and the 46th day, resulting in a fall of 19 lb. (8.6 kg.) in weight, and his venous pressure returned to normal. An *x*-ray film of the chest on the 31st day showed a slight increase in the diameter of the heart, and an early effusion in each costophrenic angle. On the 48th day the *x*-ray picture was back to normal. Between the 27th and the 30th day he received 500,000 units of penicillin twice daily, but as the organisms were proved insensitive to this, and it had no effect on his temperature, this may be regarded as ineffective and omitted from the discussion.

Ever since admission he had been receiving regular *x*-ray treatment to the antrum and secondary nodes in the left side of the neck, the dose increasing almost linearly until on the 59th day he had received a maximum of 5,100 r and a minimum of 3,660 r to the antrum and about half of this amount to the glands.

An electromyographic examination was carried out by Dr. P. Bauwens about seven months later, but nothing abnormal was found. He regarded the diagnosis of myasthenia gravis as excluded by this examination. A fractional test meal done at about the same date showed free acid in the resting juice and a hyperchlorhydric curve after histamine.

There can be no doubt that the patient suffered from a vitamin-B deficiency, leading to cardiac weakness and a proximal motor neuropathy. The time relations strongly suggest that either pyridoxine or pantothenic acid affected the neuropathy beneficially, and that aneurine hydrochloride in large doses intravenously cured the myocardial weakness. The patient was still alive when this report was drafted, and there had been no recurrence of the neuropathy, but further radium treatment for his carcinoma had been necessary.

Case 2

A woman aged 56 had for nine years noticed a lump in her right breast which, two months before attending hospital, ulcerated and was subsequently so typical of an advanced scirrhous carcinoma with secondaries in the axilla that biopsy was omitted as unnecessary. Just before *x*-ray treatment was started she noticed aching in the upper part of her back and weakness, particularly of the muscles used to hold up her head. There were no sensory symptoms or signs. On examination about one month after starting *x*-ray treatment there was definite weakness of the sternomastoids, trapezii, the extensors and flexors of the whole spine (but particularly of the cervical spine), deltoids, supraspinati and infraspinati, serratus anterior, and the ilio-psoas groups. The distal limb muscles were not affected at all. The triceps-jerks were absent, but other reflexes were present. She was unable to sit up without using her arms, and exhibited trick movements when extending her neck and thoracic spine. She had a sad "myopathic" facies, but no definite weakness of the facial muscles could be demonstrated. There was considerable generalized loss of subcutaneous fat, attributed to the ulcerating carcinoma.

Two months after starting radiotherapy an *x*-ray film of the cervical spine showed no evidence of secondary deposits, only early osteoarthritis. At the same time screening of the chest showed marked impairment of movement of the anterior portion of the left diaphragm. A month later a lumbar puncture showed a normal C.S.F. with no block and under normal pressure: total protein 31 mg. per 100 ml., globulin negative, no increase in cells, Lange and Wassermann reactions negative. Electromyography, performed about the same time, showed no spontaneous activity in the right trapezius, right deltoid, or left trapezius, but, on volition, the pattern of motor unit activity was decreased and the units were broken up as is seen in neurogenic lesions.

Radiotherapy to the breast and associated lymph nodes lasted three months and the maximum total dose approached 6,000 r to the breast and axilla. One month after the end of this treatment the mass of malignant tisssue had almost completely disappeared and her muscular weakness began to decrease. At the same time as this was noted she was also given aneurine hydrochloride by mouth, 9 mg. daily. Looking back, one can see that it would have been much more helpful if this had been prescribed two or three months earlier, as, anyway, improvement would be expected with the suppression of the carcinoma; therefore the effect of the aneurine at that particular time cannot be assessed one way or another. This improvement in muscular weakness continued slowly but fairly steadily.

Ten months later her right shoulder had become "frozen," despite physiotherapy, and the right trapezius was seen to be almost totally denervated, owing to local extension of the growth. Her other muscle weakness still existed, but to a less extent. Pyridoxine, 50 mg. intravenously twice weekly, was given until a total of 200 mg. had been reached. The patient stated that she had noticed a great improvement during this period, much more than in any other two weeks; and examination confirmed this: there seemed to have been complete recovery of the ilio-psoas group. The cervical spinal muscles were still detectably weak, however. She has continued to take 50 mg. of pyridoxine daily by mouth since then and has become almost normal, apart from the "frozen" shoulder and right trapezius paralysis.

A fractional test meal showed no free acid in the resting juice or until 30 minutes after an injection of histamine (0.5 mg.), but specimens withdrawn 30 to 50 minutes after the injection contained free acid in normal amounts.

The patient was still alive and reasonably well when this account was written, despite the presence of the carcinoma in the breast, axilla, and supraclavicular region.

Discussion

There seems to be no doubt that both conditions were causally related to the carcinoma, and in one case there is incontrovertible evidence of return to normal following vitamin-B therapy; in the other case the evidence is less strong. In both cases the weakness began before treatment with *x* rays and therefore cannot be attributed to irradiation. The possibility of erroneous diagnosis seems excluded by electromyography, which showed no evidence of myopathy, myasthenia, or anything other than neuropathy. Fasciculation was not seen in either case, nor was muscle tenderness a feature. It is possible that hypochlorhydria played some part in predisposing to vitamin-B deficiency in Case 2, but it seems more reasonable to suppose that the condition really arose from competition by the tumour for the vitamin, leading to a bodily deficiency.

Taken in conjunction with the other evidence quoted above, these two cases seem to be examples of a nosologically distinct disease due to a deficiency of vitamin B and caused by cancer indirectly. An attempt has been made to combine all these facts by the simplest hypothesis, outlined as follows:

Vitamin-B group deficiency occurs in many forms of carcinoma, but most often in carcinoma of the bronchus. At least two distinct types exist: (1) Proximal motor weakness, often with brain-stem lesions and no sensory component, and no abnormality in the C.S.F. (2) Peripheral mixed motor and sensory neuropathy with sensory phenomena predominating, and often with abnormal C.S.F. (cf. Guillain–Barré syndrome).

The first I would attribute mainly to pyridoxine deficiency; the second to deficiency of some other member of the vitamin-B group, pantothenic acid or riboflavine being the most likely. No doubt mixed types occur, since nearly always when one member of the vitamin-B group is deficient, others are also. It is not surprising, therefore, that pyruvate-tolerance tests are abnormal in most cases. Solely from the point of view of therapy, it follows that the ideal treatment is daily intravenous injections of aneurine, with other members of the vitamin-B group, including pantothenic acid and pyridoxine, in large doses. For the purpose of elucidating these syndromes, however, it would be of great value to treat some cases with pyridoxine or pantothenic acid alone, and to observe the results, being prepared to add the other vitamins if necessary.

With regard to animal experiments, a different approach is indicated. The feeding trials of Follis and Wintrobe and of Swank and Adams need to be repeated, but with the emphasis on function, not histology, and with careful assessment of motor and sensory changes by clinical examination of the living animal and by electromyography. This is really only a special case of the generalization that in medicine, except to the anatomist, details of structure are significant only in their relation to function. Swank and Adams report, for example, that the motor roots of certain pyridoxine-deficient animals were normal, but this gives no information about the presence or absence of muscle weakness, since the motor nerves might well be functionless at some point distal to the motor root, and retrograde degeneration of nerves does not occur to any great extent (though one might have expected chromatolysis of the anterior horn cells to be visible).

Summary

The importance of recognizing neuropathy in cancer patients is mentioned, and two cases of proximal motor neuropathy in association with carcinoma are described. In the first, there was also cardiac weakness similar to the mixed type of beriberi. Both cases subsequently recovered neurologically, and there is definite evidence that vitamin B was responsible, particularly pyridoxine. In both the carcinoma is still present, although it has responded to irradiation. These cases should be differentiated from cases of true peripheral neuropathy. A hypothesis based on competition for the vitamin by the tumour cells is suggested. It is also suggested that pyridoxine should be included when treating these cases in future.

My thanks are due to Mr. Maxwell Ellis, Mr. W. A. Mill, Mr. A. H. Hunt, and Dr. Worster Drought for permission to publish case reports of patients under their care. I am also indebted to Dr. M. Lederman and many of my colleagues for their co-operation, and also to Dr. Frank Sargent, who first suggested to me the theory of substrate competition.

[Since this paper was written an account of eight cases of proximal motor neuropathy in association with carcinoma of the bronchus has been published by R. A. Henson (*Proc. roy. Soc. Med.*, 1953, **46**, 859).]

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METHOD OF ESTIMATING ISONIAZID IN BIOLOGICAL FLUIDS

BY

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Several colorimetric methods have been proposed for estimating isoniazid (*iso*nicotinic acid hydrazide) in biological fluids (Kelly and Poet, 1952; Rubin *et al.*, 1952; Ginoulhiac, 1952; Smolarek and Stahl, 1953; Wojahn and Wempe, 1953; Jacobs, 1953).

The following method was developed in an attempt to improve the specificity of isoniazid estimations. It depends on the reaction between isoniazid and picryl chloride (2-chloro, 1,3,5-trinitrobenzene) to form a coloured compound, which may be measured photoelectrically.

While our work was in progress a method for the estimation of isoniazid with picryl chloride was described (Kirschbaum, 1952), but not its application to biological fluids.

Method for Plasma

Reagents.—Whenever available, all reagents used were of analytical reagent grade.

10% (W/V) sodium tungstate.$2H_2O$
2/3N sulphuric acid
N sodium hydroxide
N/10 hydrochloric acid
Ammonium sulphate
n-butanol 1 part, diethyl ether 3 parts
Phosphate buffer *p*H 7: 60 ml. of M/5 disodium hydrogen phosphate added to 40 ml. of M/5 potassium dihydrogen phosphate.
Phosphate buffer *p*H 6.5: 30 ml. of M/5 disodium hydrogen phosphate added to 70 ml. of M/5 potassium dihydrogen phosphate
5N acetic acid
Picryl chloride (Hopkin and Williams). This reagent should be washed twice in distilled water, recrystallized twice from chloroform, and air-dried. It is stored in a dark bottle in the refrigerator.

A freshly prepared solution—35 mg. of picryl chloride in 10 ml. of ethanol—is required for the estimation.

Procedure

Plasma (heparinized) from 10 ml. of blood is required for the estimation.

Protein Precipitation.—8 ml. of distilled water, 4 ml. of plasma, and 2 ml. of sodium tungstate solution are measured into a 1-oz. (30-ml.) screw-capped bottle. After mixing well, 2 ml. of 2/3N sulphuric acid is slowly added, with constant shaking. The lid is screwed lightly in position, and the bottle placed in a boiling-water bath for five minutes, cooled, and centrifuged for 10 to 15 minutes—that is, enough to make possible the withdrawal of 12 ml. of supernatant protein-free fluid.

Extraction of Isoniazid into Butanol–Ether Mixture.—11 g. of ammonium sulphate, 0.5 ml. of N sodium hydroxide

solution, 1 ml. of phosphate buffer *p*H 7, 40 ml. of butanol–ether mixture, and 12 ml. of supernatant protein-free fluid are measured into a glass-stoppered 2-oz. (60-ml.) bottle. The bottle is shaken vigorously for five minutes (mechanically) and then allowed to stand until the butanol–ether and aqueous phases separate. The butanol–ether phase is transferred as completely as possible to a fresh 2-oz. glass-stoppered bottle.

Extraction of Isoniazid into Hydrochloric Acid.—The butanol–ether extract is shaken for two to three minutes with two separate volumes of 5 ml. of N/10 hydrochloric acid. The combined acid extracts are then placed in a 6 by 1 in. (15 by 2.5 cm.) test-tube.

Colour Reaction.—1 ml. of N sodium hydroxide and then 2 ml. of phosphate buffer *p*H 6.5 are added to the acid extract. After mixing well, 0.5 ml. of freshly prepared picryl chloride solution is added and the tube heated for 20 minutes in a boiling-water bath. The tube is cooled and 0.4 ml. of 5N acetic acid is added, followed by 6 ml. of *n*-butanol. After being shaken for approximately one minute the tube is centrifuged and the butanol phase transferred to a test-tube, two drops of ethanol being added to prevent any cloudiness due to water droplets.

Colour Measurement.—Readings are made against water in a Hilger absorptiometer, using a 4-cm. (8-ml.) light-path cell and an Ilford blue-green filter No. 603 (absorption maximum 485 mμ).

Standard Curve.—Results are calculated by comparison with a standard curve. This is prepared from readings obtained by applying the method to known freshly prepared solutions of 0, 4 μg., 8 μg., and 16 μg. of isoniazid, each level in 4 ml. of pooled, non-haemolysed plasma from blood transfusion material. The reproducibility of the method is satisfactory: the absorptiometer readings are linearly related to the amounts of isoniazid present within the range 0 to 20 μg. The standard deviation of a single estimation is about ± 10%. It is necessary to estimate unknown samples and standard samples concurrently.

Method for Urine

The same method is used as for plasma, but protein precipitation is omitted.

Test samples are read against standard aqueous isoniazid solutions treated in the same way.

Specificity of Method

Metabolic Products of Isoniazid Ingestion

The urine of human subjects after isoniazid ingestion is known to contain isoniazid, *iso*nicotinic acid, and *iso*nicotinoyl glycine (Cuthbertson *et al.*, 1953). *Iso*nicotinamide was not detected, but could have been present undetected in amounts of up to about 5% of the dose. The reactions of these substances with picryl chloride have been described (Cuthbertson *et al.*, 1953). Quantities of 150 μg. of each of the last three substances do not interfere in the recommended method.

Another metabolic product of isoniazid ingestion is also present in human urine, but its nature is unknown. By paper chromatography of concentrated urine solutions using water-saturated *n*-butanol as developing solvent, this substance has approximately the same R_F value as *iso*nicotinamide. It reacts with picryl chloride to form a red-coloured compound at alkaline *p*H and a yellow-coloured compound at acid *p*H, but does not react with the cyanogen bromide–pyrazolone or cyanogen bromide–benzidine reagents in the same way as *iso*nicotinamide (Cuthbertson *et al.*, 1953).

Since this substance reacts with picryl chloride similarly to *iso*nicotinic acid and *iso*nicotinamide, it is unlikely to interfere in the determination of isoniazid by our method. This assumption is supported by the fact that after isoniazid ingestion some 24-hour human urine samples contain little or no isoniazid, as shown by this method, but do contain appreciable amounts of the unidentified substance, as shown by chromatography.

Wojahn and Wempe (1953) have shown that isoniazid combines through its hydrazide group with an unknown substance or substances in plasma and urine to form microbiologically inactive or less active compounds. We have no direct evidence to show whether or not these compounds, if different from the unknown metabolite described above, interfere in our method. Circumstantial evidence indicates that they interfere only slightly, if at all. Smolarek and Stahl (1953), using a method that does not measure this type of "bound" isoniazid, found that the average 24-hour urine excretion of free isoniazid in five human subjects receiving a single 500-mg. oral dose of isoniazid was 17.5% of the dose. The individual values varied between 13.6% and 22.5% of the dose. We found that the 24-hour urine contents of isoniazid in two human subjects each receiving 250 mg. of isoniazid orally every 12 hours were 21% and 22% of the dose. Furthermore, approximate assessments of the isoniazid content of urine samples from chromatographic evidence agree with actual estimations.

Since *iso*nicotinic acid is a metabolic product of isoniazid ingestion in human subjects, hydrazine could also be liberated. Hydrazine reacts with picryl chloride to form hexanitrohydroazobenzene (Kulberg and Cherkesov, 1952), the light absorption of which would be measured by this technique. However, Kelly and Poet (1952) and Kelly *et al.* (1952) have not detected the presence of free hydrazine in the body fluids of the animals they studied. Using their method, we were unable to detect free hydrazine in the plasma of human subjects receiving orally 200 mg. of isoniazid per subject, or in the plasma of guinea-pigs (body weight 380 to 420 g.) receiving orally 10 mg. of isoniazid per guinea-pig, at ½, 1, 2, 4, or 7 hours after the dose. Also 24-hour urine samples from human subjects receiving 500 mg. of isoniazid orally contained no free hydrazine.

Streptomycin and p-Aminosalicylic Acid

Experiments were performed to detect any possible interference with the picryl chloride method by streptomycin or *p*-aminosalicylic acid.

In aqueous solutions of isoniazid the addition of 500 μg. of streptomycin per ml. caused no increase in the readings obtained.

p-Aminosalicylic acid was found to interfere even in relatively low concentrations. For this reason it was possible to perform isoniazid assays only on patients not at the time receiving any *p*-aminosalicylic acid, but streptomycin therapy was not a factor of importance in this connexion.

Results

Plasma

Isoniazid was estimated in the plasma of 24 patients. Twenty-two received 100 mg. and two 150 mg. of isoniazid orally every twelve hours. Table I gives each patient's dose in mg. of isoniazid per kg. body weight.

Blood samples were taken by venepuncture shortly before the morning dose of the drug, and three further samples were withdrawn at intervals of 30, 60, and 120 minutes afterwards. Preliminary tests had soon shown that the picryl chloride method was not sensitive enough to detect any isoniazid in plasma twelve hours after the last dose, and so it was considered permissible to treat the early morning plasma of each patient as a "blank."

Table I shows the results obtained from these patients. In general, the plasma levels are somewhat lower than the figures quoted in previous publications (Elmendorf *et al.*, 1952; Rubin *et al.*, 1952), and the highest level was almost always found 30 or 60 minutes after the dose.

In 10 patients receiving 1.15 to 1.5 mg. of isoniazid per kg. body weight the average level of isoniazid estimated 30 minutes after the dose was 0.7 μg./ml., 60 minutes after the dose 0.8 μg./ml., and 120 minutes after the dose 0.4 μg./ml. For 14 patients receiving 1.55 to 3.65 mg. of isoniazid per kg. body weight the corresponding 30-minute,

TABLE I.—*Concentrations of Isoniazid in the Plasma of Patients After Oral Administration*

Case No.	Dose in mg./kg. Body Weight	Plasma Level of Isoniazid in μg./ml. at Intervals, after the Dose, of		
		30 Minutes	60 Minutes	120 Minutes
1	1·15	1·6	0·8	0·5
2	1·35	0·8	1·0	0·9
3	1·35	1·6	1·3	0·8
4	1·35	0·0	0·0	0·0
5	1·35	0·0	1·3	0·5
6	1·35	1·1	0·9	0·0
7	1·35	0·0	1·0	0·1
8	1·45	1·1	0·9	1·1
9	1·50	0·5	1·0	1·2
10	1·50	0·0	0·0	0·0
11	1·55	1·0	1·1	0·9
12	1·55	1·0	0·7	0·5
13	1·55	2·0	1·5	0·8
14	1·55	2·8	4·0	3·2
15	1·55	0·6	1·5	1·0
16	1·65	1·3	1·0	0·6
17	1·65	0·5	0·5	0·8
18	1·75	0·9	1·5	2·6
19	1·80	0·2	1·2	0·4
20	1·95	2·0	0·9	0·6
21	1·95	0·0	0·0	0·0
22	2·05	0·8	1·9	2·1
23	2·60	0·2	1·9	0·6
24	3·65	1·0	1·0	0·6
10 R	1·50	0·5	0·2	0·0
21 R	1·95	0·0	0·0	0·5

The plasma isoniazid concentration of Cases 10 and 21 were redetermined three months later as shown under 10 R and 21 R.

60-minute, and 120-minute values were 1.0 μg./ml., 1.3 μg./ml., and 1.0 μg./ml.

Three of the 24 patients (Cases 4, 10, and 21) had no detectable isoniazid in any of the blood samples. Nothing in their clinical condition suggested a disturbance of intestinal absorption, and examination of urine for isoniazid and its metabolites was undertaken in Cases 10 U and 21 U (Table II). This subject is considered in the discussion of

TABLE II.—*Urinary Excretion of Isoniazid.* (*a*) 100 *mg. Isoniazid, Administered Orally 12-hourly;* (*b*) 250 *mg. Isoniazid, Administered Orally 12-hourly*

Case No.	mg. Isoniazid per kg. Body Weight	μg./ml. Isoniazid in Urine	Total Isoniazid Excreted in 24 Hours (mg.)	% of Dose Excreted in 24 Hours
(*a*) 25 U	3·3	13	9·7	4·8
26 U	3·5	20	35·0	17·5
27 U	2·7	18·5	32·0	16
28 U	2·3	6·2	11·5	5·7
29 U	3·2	8·0	17·4	8·7
30 U	3·1	8·4	8·0	4·0
31 U	3·9	4·3	5·3	2·6
10 U	3·0	2·0	3·0	1·5
21 U	3·9	2·6	5·7	2·8
			Average	7·1
(*b*) 28 U	5·7	61	103	21·0
29 U	8·0	42	110	22·0

results of urine assays. Three months later, blood curves were repeated on two of these patients (Nos. 10 R and 21 R), who were still in hospital. These two curves are very similar to those obtained on the first occasion. In both patients the highest level attained was 0.5 μg./ml., and this was present in only one specimen from each patient.

Urine

The results shown in Table II (*a*) were obtained from nine patients receiving 100 mg. of isoniazid 12-hourly. Whenever possible a 24-hour specimen of urine for use as a "blank" was collected before isoniazid therapy was begun, and the test estimations were performed on aliquots of 24-hour specimens of urine collected during treatment.

The amount of the dose excreted as isoniazid during 24 hours varied widely (1.5% to 17.5%, average 7.1%). These values are appreciably lower than those found by Elmendorf *et al.* (1952), using the assay method of Kelly and Poet (1952). In six patients receiving 3 mg. of isoniazid per kg. body weight, they found the 24-hour urinary excretion of isoniazid lay between 47.8% and 70.7% of the dose. Our results thus confirm that the method of Kelly and Poet measures something besides isoniazid (Smolarek and Stahl, 1953; Wojahn and Wempe, 1953; Cuthbertson *et al.*, 1953). Samples 10 U and 21 U (Table II (*a*)) are urine samples from the patients whose blood values are shown in Table I as 10 and 21 and 10 R and 21R. In these two patients the very low excretion values, together with the low blood levels suggested some defect of absorption, but chromatographic analysis (Cuthbertson *et al.*, 1953), of the two urine samples revealed the presence of the metabolites of isoniazid (*iso*nicotinoylglycine, *iso*nicotinic acid, and the unidentified metabolite) in approximately the same amounts as contained in the urine of patients with higher isoniazid levels in blood and urine. Assessment of their clinical response to isoniazid was rendered difficult, for both the patients were also receiving streptomycin.

Patients whose urine samples are given as 28 U and 29 U were subsequently given 250 mg. of isoniazid twelve-hourly. There was an appreciable rise in percentage of the dose excreted as isoniazid during the succeeding 24-hour period (Table II (*b*)).

Further assessment of the method is desirable and should lead to improved evaluations of results obtained by it. It is hoped that the description given here of both method and results may be of use to those who wish to carry the matter further.

Summary

A colorimetric method is described for estimating isoniazid in biological fluids by means of picryl chloride.

The specificity of the method is assessed with reference to the metabolites of isoniazid.

Results are given for the amounts of isoniazid in plasma and urine from patients receiving the drug.

We wish to thank the physicians and surgeons of the Brompton Hospital for permission to investigate the samples from their patients; Dr. R. N. Johnston, medical registrar, for his great assistance in the collection of samples; and Miss E. Harris and Mr. F. W. Price for technical assistance.

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The professor of medicine at Duke University, North Carolina, Dr. James V. Warren, is to visit Kenya to perform research work on giraffes. The object of this research is to aid those who are designing "G-suits" (gravity suits) worn by the pilots of high-speed jet aeroplanes. In pulling out of power dives or other manœuvres at high speeds pilots are subjected to pressure eight or nine times the force of gravity. It is generally believed that a pressure of 8 G is the maximum that a pilot can withstand. The G-suits are pressurized and designed to offset the violent pressure changes which cause a reduced flow of blood to the brain and consequent black-outs. Dr. Warren believes that the giraffe, with its head a considerable distance from its heart, has at all times to meet the situation that man faces when he is subjected to centrifugal force in military planes making fast turns and dives. "Maybe," Dr. Warren is reported to have said, "the giraffe has some sort of booster mechanism that helps its heart."—*U.S.A. in Review*, February 24, 1954.

VALUE OF STRICT DIETING, DRUGS, AND "ROBADEN" IN PEPTIC ULCERATION

BY

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Recent papers on gastric and duodenal ulceration express conflicting views on the value of many of the therapeutic measures customarily used in the conservative (non-surgical) treatment of the two diseases. Nicol (1939), Ronald (1939), and Lawrence (1952) found that rest in hospital on a light diet or even a normal hospital diet gave results as good as those obtained in hospital on a strict "ulcer" diet with antacids and belladonna, whilst Doll and Pygott (1952) found that cases treated on a "gastric" diet in hospital fared better than those on ambulatory treatment with a "convalescent" diet. They were undecided whether the physical and mental rest or the supervised strict dieting was the important factor, although they showed that phenobarbitone and vitamin C had no influence on the rate of ulcer healing. Martin and Lewis (1949), as a result of a 10–14-year follow-up of cases, concluded that medical treatment had *no* influence on the natural history of gastric and duodenal ulceration. Morton Gill (1947) found that the treatment of gastric ulcers with subcutaneous injections of sterile water whilst the patients were ambulant and on a normal diet gave results as good as those achieved with orthodox treatment.

The great importance of anxiety and mental stress in the pathogenesis and in the precipitation of relapse of peptic ulceration, and particularly of duodenal ulceration, is now generally accepted (Davies and Wilson, 1937; Nicol, 1939, 1942; Gill, 1947).

Many authors have stressed the importance of controlling gastric acidity. Nicol (1939) and Douthwaite (1939, 1947) showed that full doses of belladonna and the usual antacids, given by mouth, have no great effect on the diurnal gastric acidity, and Douthwaite and Thorne (1951) showed that hexamethonium was equally ineffective by day. Nocturnal acid secretion is, however, largely governed by neural mechanisms, and night acid can be controlled by hexamethonium (Kay and Smith, 1950) and full doses of belladonna (Riddell, 1951). Diurnal acid secretion can be controlled effectively by a continuous milk drip (Winkelstein, 1932) and by the continuous sucking of milk-alkali tablets (Douthwaite and Batty Shaw, 1952).

Regarding the prognosis of peptic ulceration most authors are gloomy. Nicol (1942), in a four-year follow-up of 389 cases, found that only 17% remained symptom-free, although a further 41% were well enough to remain at work on a diet. Martin and Lewis (1949) in a 10–14 year follow-up found 44% of gastric ulcers and 33% of duodenal ulcers inactive (no ulcer dyspepsia for the preceding five years). Barsby (1951) followed up her gastric ulcer subjects with the gastroscope until complete healing had taken place, but found that 43% had a recurrence at the original site and a further 9% at other sites.

It is therefore not surprising that many clinicians are sceptical of the value of many of the traditional drugs and regimes used in the treatment of peptic ulceration. Todd (1949, 1951, 1952) cast doubt on the value of rest in bed, absence from work, strict dieting, sedation, and the avoidance of alcohol and tobacco. He advocated the liberal use of antacid tablets.

The possibility that in peptic ulcer subjects a "mucosa protecting" substance might be lacking has excited the interest of clinicians for some years, and recently "robaden" has been claimed by many Continental authors to possess ulcer-healing and mucosa-protecting properties (Neumann, 1948; Barfred, 1950; Schmassmann, 1951; Burghartz, 1951; etc.). Robaden is described by the makers as protein-free extracts obtained from the stomach and small intestine of freshly slaughtered young animals. The water-soluble part of the extract is used by injection and the water-insoluble part is taken by mouth in tablet form. The British literature contains few references to robaden. Hubacher (1946) claimed very good results in a 16-months follow-up of 54 patients treated with robaden whilst ambulant on a normal diet. There was, however, no control series. Stolte (1950) gave, impartially, robaden or a placebo to 101 patients with gastric or duodenal ulceration whilst they carried on with their normal work and diet. He found that, from the clinical and radiological points of view, there was no difference in the percentage of success. A possible criticism of this work is, however, that the injections and tablets of robaden were not given concurrently, as recommended by the makers.

In 1948 I decided to investigate the value of robaden in treatment and also whether strict dieting together with the usual gastric drugs whilst the patient was on strict rest in bed in hospital had any advantages over treatment in hospital on a light diet and partial ambulation.

Material and Method

I had the use of a male gastric ward of 10 beds, into which I admitted proved or suspected ulcer cases from the out-patient department. Those considered to be in need of surgery when first seen were not included in the series. The final diagnosis of peptic ulceration was made on radiological evidence supported, in a few cases, by gastroscopy. On admission, if not already done in the out-patient department, a barium-meal *x*-ray examination and an alcohol-histamine fractional test meal were performed, and during the fourth week in hospital three consecutive stools were examined for occult blood and the barium-meal examination was repeated. Almost all the radiology in the series was done by one radiologist.

The series comprised 27 patients with gastric ulcer, of whom five were female and three also had a duodenal ulcer, and 87 patients with a duodenal ulcer, of whom two were female and three also had a gastric ulcer.

On the patients' admission their names were put on a rota which decided by which of four methods they were to be treated. The four methods were: (i) strict gastric diet plus drugs, on strict rest in bed (bathroom freedom allowed once a day); (ii) as above, with the addition of robaden; (iii) post-ulcer diet whilst allowed up and about two hours daily; and (iv) as in (iii), with the addition of robaden. (Details of the diets and drugs used are given in the Appendix.)

Patients on robaden were given each morning for 21 days 1 ml. of the appropriate injection (for gastric or duodenal ulcer as the case might be) intramuscularly into the lateral aspect of the thigh, together with one robaden tablet three times a day before meals for seven weeks and then one tablet daily for the first ten days in each month for three

months. Patients on robaden whose pain persisted for longer than a few days after admission had their daily injection increased to 2 ml. for a week. Cases *not* on robaden were given placebo injections and tablets on the same schedule as the robaden cases. After four weeks' in-patient treatment the patients were sent home on their allotted regime (see Appendix) for three weeks, following which they were seen by me personally. If all was well they were then advised to return to work while keeping to their treatment. They were asked to come and see me every three months, and were encouraged to come up earlier if they had a recurrence of symptoms.

The following study deals with those patients whom I followed up for at least six months. The final information about the patients was obtained by interview in half the number. The remainder, who did not respond to an invitation to attend, replied to a questionary (see Appendix).

It is thought that the patients in each therapeutic group are comparable, as can be seen from Table I.

TABLE I

Treatment Group	No. of Cases		Average Length (Years) of Ulcer Symptoms		Average Age (Years)	
	G.U.	D.U.	G.U.	D.U.	G.U.	D.U.
1. Robaden + strict diet	6	20	7	5½	49	39
2. Strict diet ..	10	28	5	6	46	40
3. Robaden + post-ulcer diet ..	7	19	5	8	46	43
4. Post-ulcer diet ..	4	20	5	9	46	46

The history of previous treatment and complications, and also the alcohol and tobacco habits, were comparable in each of the groups.

Results

A. Patients with Gastric Ulceration

Comparison of the results between the four therapeutic groups was made in a number of ways. The disappearance of pain and tenderness was not found to be helpful, as these almost always disappeared within a few days of admission, whilst the absence of occult blood during the fourth week in hospital (at least two specimens examined) and the return of the radiological picture to normal were not of much value in assessing the prognosis. Thus, of those followed up for at least six months, only five had negative occult blood tests, and two of these had a recurrence of ulceration after 30 and 32 months (average follow-up time in those with no recurrence, 29 months), while 20 patients returned to radiological normality, of whom 5 relapsed (average time to relapse, 14 months; average follow-up time, 28 months). It is, however, of interest that of the 20 patients who returned to normal, 9 were on post-ulcer diet and robaden or post-ulcer diet alone, and none relapsed (average follow-up time, 30 months).

The figures in Table II give no indication that robaden expedites healing.

TABLE II.—*Details of Radiological Results*

Treatment Group	No. Followed until Healed Radiologically	Average Healing Time	Average No. of Barium-meal X-ray Examinations
1. Strict diet + robaden	4	9 weeks	4
2. Strict diet alone	8	9 „	4
3. Post-ulcer diet + robaden ..	6	19 „	3·2
4. Post-ulcer diet alone ..	3	7 „	2·3

1. *Clinical relapse rate* amongst the cases followed up for at least six months, severe enough to need dieting while they were off work (Table III). Those who were referred for surgical treatment during their initial admission to hospital, and also those who, because they did not respond to the allotted regime, were given stricter treatment, are excluded.

The figures in Table III can be treated in another way—dividing the cases into four further groups: (A) those treated on diet alone (strict diet alone and post-ulcer diet alone); (B) those given robaden (strict diet+robaden and post-ulcer diet+robaden); (C) those treated with a strict ulcer diet (strict diet+robaden and strict diet alone); and (D) those given a post-ulcer diet (post-ulcer diet+robaden and post-ulcer diet alone) (Table IV).

TABLE III

Treatment Group	No. of Cases Followed Up at Least 6 Months	No. of Cases which Relapsed	Average Length of Follow-up in those Not Relapsing	Average Time to Relapse	Relapse
1. Strict diet + robaden ..	5	3	20 months	7 months	60%
2. Strict diet alone	7	3	26 „	12 „	43%
3. Post-ulcer diet + robaden ..	5	0	34 „	—	0
4. Post-ulcer diet alone ..	4	1	25 „	23 months	25%

TABLE IV

Group	No. of Cases Followed Up at Least 6 Months	No. of Cases which Relapsed	Average Length of Follow-up in those not Relapsing	Average Time to Relapse	Relapse
A. Diet	11	4	26 months	15 months	36%
B. Robaden ..	10	3	29 „	7 „	30%
C. Strict diet ..	12	6	23 „	9½ „	50%
D. Post-ulcer diet	9	1	31 „	23 „	11%

2. Two patients were given stricter treatment because they were not responding to their allotted regime. One was in group 2 and the other in group 3. Two cases came to surgery during their initial admission—one in group 1 and the other in group 3.

3. It is considered fair to compare each therapeutic group on the number of "failures" in each group. By failures is meant those who had a clinical relapse, those who came to surgery during their initial admission, and those who, because they were not responding to the allotted treatment, were put on to a stricter regime (Table V).

TABLE V

Treatment Group	Average Length of Follow-up	"Failures"	
		No.	%
1. Strict diet + robaden ..	20 months	4 out of 6	67
2. Strict diet alone ..	26 „	4 „ „ 8	50
3. Post-ulcer diet + robaden	34 „	2 „ „ 7	29
4. Post-ulcer diet alone ..	25 „	1 „ „ 4	25

Treating these figures in a different way gives the results shown in Table VI.

TABLE VI

Group	Average Length of Follow-up	"Failures"	
		No.	%
A. Diet	26 months	5 out of 12	42
B. Robaden	30 „	6 „ „ 13	46
C. Strict diet	24 „	8 „ „ 14	57
D. Post-ulcer diet ..	31 „	3 „ „ 11	27

The average gain in weight from the first to the last interview among those treated on a strict diet was 3 lb. (1.4 kg.) (average of 16 cases), whilst those treated on a post-ulcer diet gained 13 lb. (5.9 kg.) (average of 10 cases).

Comment.—These figures suggest that, of the regimes tested, a post-ulcer diet at rest in hospital gives the best results, and no evidence was found that robaden was of value in treatment. It is realized, however, that the series is a small one.

B. Patients with Duodenal Ulceration

1. Very strict radiological criteria were used before pronouncing a duodenal ulcer as having healed—namely, a cap normal in shape and with no demonstrable spasm or ulcer crater. Table VII gives details of the radiological results.

TABLE VII.—*Details of Radiological Results*

Treatment Group	No. who had Repeated Barium Meal X-ray Exams	No. Followed Until Healed Radiologically	Average Healing Time	Average No. of Barium Meal X-ray Exams
1. Strict diet+robaden	18	3	6 weeks	3·2
2. Strict diet alone ..	23	10	15 „	2·6
3. Post-ulcer diet+robaden	17	3	10 „	3·0
4. Post-ulcer diet alone	16	5	8 „	2·9

2. *Clinical Relapse Rate.*—Amongst the cases followed-up for at least six months, severe enough to need strict dieting while they were off work. Those who were referred for surgical treatment during their initial admission and also those who, because they did not respond to the allotted regime, were given stricter treatment are excluded.

TABLE VIII

Treatment Group	No. of Cases Followed Up at Least 6 Months	No. of Cases which Relapsed	Average Length of Follow Up in those Not Relapsing	Average Time to Relapse	Relapse
1. Strict diet+robaden ..	13	6	27 months	21 months	46%
2. Strict diet alone	17	4	27 „	9 „	24%
3. Post-ulcer diet+robaden ..	9	2	35 „	7 „	22%
4. Post-ulcer diet alone ..	15	7	25 „	16 „	47%

Treating these figures in a different way, by dividing the cases into the four groups: (A) "diet" (strict diet alone and post-ulcer diet alone), (B) "robaden" (strict diet+robaden and post-ulcer diet+robaden), (C) "strict diet" (strict diet +robaden and strict diet alone), and (D) "post-ulcer diet" (post-ulcer diet+robaden and post-ulcer diet alone), the results shown in Table IX are obtained.

TABLE IX

Group	No. of Cases Followed Up at Least 6 Months	No. of Cases which Relapsed	Average Length of Follow Up in those Not Relapsing	Average Time to Relapse	Relapse
A. Diet	32	11	26 months	13 months	34%
B. Robaden ..	22	8	31 „	17 „	36½
C. Strict diet ..	30	10	27 „	16 „	33⅓
D. Post-ulcer diet	24	9	29½ „	14 „	37½

The figures in Tables VIII and IX do not demonstrate a clear-cut advantage of any of the four therapeutic regimes used.

3. Ten patients, because they were not responding to their allotted regime, were given stricter treatment (strict diet+continuous milk drip): one was in group 1, two were in group 2, five were in group 3, and two were in group 4.

In this series the prognosis in cases given continuous-milk-drip treatment was poor, but these patients, together with the nine described below, represented the hard core who did not respond at all to their allotted treatment.

4. Nine cases, owing to lack of response to treatment, came to surgery during their initial admission: three were in group 1, three in group 2, one in group 3, and two in group 4.

5. *Failures in Each Therapeutic Group.*—The figures comprise those who relapsed clinically, those who came to surgery during their initial admission, and those who, because they were not responding to the allotted treatment, were given a stricter regime. If in the last four groups in Table X the follow-up time is increased to 31 months the estimated failure rates (simple arithmetical proportions) are: diet, 58%; robaden, 56%; strict diet, 56%; and post-ulcer diet, 59%. As regards efficacy of treatment, these figures suggest that there is little to choose between the four therapeutic regimes.

TABLE X

Group	Average Length of Follow-up in Non-failures	Failures	
		No.	%
1. Strict diet+robaden ..	27 months	10 out of 17	59
2. Strict diet alone ..	27 „	9 „ „ 22	41
3. Post-ulcer diet+robaden	35 „	8 „ „ 15	53
4. Post-ulcer diet alone ..	25 „	11 „ „ 19	58
A. Diet	26 „	20 „ „ 41	49
B. Robaden	31 „	18 „ „ 32	56
C. Strict diet	27 „	19 „ „ 39	49
D. Post-ulcer diet ..	29 „	19 „ „ 34	56

6. The absence of occult blood in the stool during the fourth week in hospital was not found to be of great prognostic importance, but the return of the duodenal cap to normal carried a good prognosis. With a follow-up of at least six months a total of 18 of the duodenal ulcer cases returned to a normal cap on radioscopy at some period (average follow-up time, 29 months), and only three of these had a clinical relapse after an average of 25 months' freedom, although there were four radiological relapses (symptomless) after an average of 14½ months.

7. The average gain in weight from the initial interview to the last one among those patients treated on a strict diet was 3.9 lb. (1.8 kg.), whilst the post-ulcer diet group gained 4.9 lb. (2.2 kg.).

Conclusions

These results support the findings of Nicol (1939), Ronald (1939), and Lawrence (1952) that rest in hospital on a light diet gives results as good as those achieved by rest in hospital on a strict "ulcer" diet with belladonna and antacids. As Doll and Pygott (1952) have found that cases treated on a "gastric" diet in hospital did better than those on ambulatory treatment and a "convalescent" diet, the conclusion can be drawn that the important factors in any successful therapeutic regime are mental and/or physical relaxation, together with the natural tendency for clinical remissions to occur in peptic ulceration.

In this country, at present, most people can best obtain this beneficial relaxation in a hospital ward where suitable food is provided, there is freedom from domestic tension, and financial worries are in most cases absent, owing to the National Insurance. It is felt that small gastric wards are an advantage: the patient has a feeling of individuality, whilst at the same time a community spirit is fostered. An occasional patient, of course, never settles down to ward life, and in these instances it is doubtful whether it is worth persevering with in-patient medical treatment.

My present routine is to treat patients with peptic ulceration in hospital on a "post-ulcer" diet. They spend most of their time in bed, but are allowed bathroom freedom and are up and about for two to three hours daily. Each patient has a supply of magnesium trisilicate on his locker, and he is encouraged to help himself to a dose whenever he has pain or discomfort. He spends a month in the ward, after which he continues resting at home on the same diet for a further

three weeks. He is then seen again and almost always advised to restart his work.

The occasional patient who fails to respond to this regime will need stricter treatment, such as a continuous milk drip or the continuous sucking of milk-alkali tablets, but my experience is that most of these refractory cases will need surgery within a few months.

Regarding after-care, it is suggested that the patient continues with his post-ulcer diet while back at work, avoiding excessive smoking and alcoholic indulgence. He should be encouraged to cultivate a calm and philosophical attitude to the stresses and strain of life, and he should, when he has discomfort, take freely of one or other of the harmless antacids as suggested by Todd (1952). In view of the high relapse rate in peptic ulceration, whatever medical treatment one gives, resort to surgery should not be delayed unduly. My practice is to advise surgery (provided there are no contraindications) if the patient relapses after one or at most two courses of medical treatment.

If this simple treatment of peptic ulceration gains favour much labour will be saved in preparing complicated diets and there will be saving on the cost of drugs. A good library, wireless, facilities for card games, and television will help to pass the time. Conventional occupational therapy is, I find, not popular with peptic ulcer patients.

Regarding robaden, I could find no clear evidence of its value. However, the patients treated with robaden were given it for only five months, and it is possible that if it had been given for a longer period beneficial effects might have been seen.

Summary

A total of 111 patients with peptic ulceration were treated in hospital and divided impartially into four therapeutic groups: (1) strict ulcer diet + robaden; (2) strict ulcer diet alone; (3) post-ulcer diet + robaden; and (4) post-ulcer diet alone. As a result of a follow-up study it is concluded that treatment on a post-ulcer diet gives results as good as those obtained with the other three regimes, and it is suggested that the important factors in any successful therapeutic regime for peptic ulceration are mental and/or physical relaxation, which assist the natural tendency for remissions to occur.

My thanks go to Dr. Stanley Nowell for the radiology; to Dr. John Forbes, who originally worked out the diets, for advice; to Professor Scarborough for advice; to the house-physicians who have kept such scrupulous notes; and to Sister J. Roberts, who instilled the right spirit into the ward and saw that the patients kept to their allotted regime.

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APPENDIX

Regime followed by those patients treated on "strict diet."

Regime A: Strict Rest in Bed (Bathroom Freedom Once Daily)

On waking.—A glass of milk to be sipped slowly.

8 a.m.—A lightly boiled, poached, or scrambled egg. Four thin half-slices of toast or bread-and-butter. A cup of milk flavoured with tea and sugar.

10 a.m.—A glass of milk to be sipped slowly. Two digestive biscuits or rusks.

12 noon.—A small portion of boiled or roast chicken; or of steamed, boiled, or grilled white fish; or of tender steak or chop; or of tripe, calf's heart, or liver. Two heaped tablespoonfuls of mashed creamed potato. A glass of milk.

2 p.m.—A glass of milk to be sipped slowly. Two digestive biscuits or rusks.

4 p.m.—A cup of milk flavoured with tea and sugar. Four half-slices of thin bread-and-butter. A portion of plain sponge cake.

6 p.m.—A moderate amount of rice, macaroni, cornflour, arrowroot, or some other milk pudding. A glass of milk.

8 p.m.—A glass of milk to be sipped slowly.

10 p.m. (if awake).—A glass of milk to be sipped slowly.

During the night the patient should be given a drink of milk or cocoa if he wakes up.

No condiments are allowed. All food must be chewed carefully and the month rinsed afterwards and kept clean.

Drugs (No other drugs are to be given without the doctor's orders).—(1) Phenobarbitone, 1 gr. (65 mg.) b.d. (2) Laevohyoscyamine, 1/120 gr. (0.54 mg.) b.d. (3) Olive oil, 1 dr. (3.5 ml.) t.i.d., after the 8 a.m., noon, and 6 p.m. feeds. (4) Soluble amylobarbitone (sodium amytal) 3 gr. (0.2 g.) nocte p.r.n. (if patient awake). (5) Liquid paraffin or an enema may be given for constipation. (6) A teaspoonful of magnesium trisilicate two-hourly, half an hour after each feed, and two teaspoonfuls last thing at night.

After three weeks the patients went on to the following diet:

Regime B: Bathroom Freedom and Up and About Two Hours Daily

Breakfast.—Small portion of porridge with milk or cream and sugar if desired. Bread or toast with butter and marmalade. A lightly boiled, poached, or scrambled egg. A cup of weak tea with milk and sugar.

10.30 to 11 a.m.—A glass of milk with biscuits or rusks.

Dinner.—4 oz. (113 g.) of fish, chicken, game, beef, chop, steak, mutton, or lamb. Boiled, baked, or mashed creamed potato. A small milk pudding. Milk or water to drink.

Tea.—A cup of weak tea with milk and sugar. Bread-and-butter. Jelly or plain cake.

Supper.—Cold meat or tongue, boiled or grilled fish. Bread-and-butter. Puree of prunes, apples, or other fruit, flavoured with milk and sugar. Milk or water to drink.

8 to 9 p.m.—A glass of milk.

Drugs.—As in Regime A.

The patient should eat slowly, chewing all food carefully.

After a week on this regime, sieved vegetables should be added to the midday meal, and, after a further week, ordinary cooked vegetables allowed.

Similarly, after the first week, the fruit at the evening meal need not be sieved, but the patient should avoid all skins and pips.

After a further week the patients went home with a copy of this regime, which they were asked to follow until seen at the out-patient department three weeks later, when they were given a copy of the following "post-ulcer diet," which they were advised to keep to whilst working. This diet is also the one followed from the start by the groups treated on "post-ulcer diet" (one month in hospital and then three weeks at home, spending most of the time resting in bed but from the beginning allowed bathroom freedom and to be up and about two hours a day).

Regime C: Ordinary Food Should be Taken with Certain Reservations

1. *No roughage.* Avoid all pips and skins of fruit, unripe fruit, nuts, currants, raisins, figs, raw vegetables, fibrous vegetables (celery, etc.), and gristly meat.

2. *No irritants. Avoid* such things as hot gravies, spices, vinegar, lemon juice, pepper, mustard, curry, pickles, chutney, and strong hot tea or coffee. Take salt in strict moderation. Take alcohol in strict moderation only. *Avoid* all drugs and patent medicine, especially aspirins and strong purgatives (see below). Smoking should be indulged in only after meals and in strict moderation (five cigarettes, or three small pipefuls daily).

3. *Overeating at one meal is as bad as going for long periods without food.* Both are harmful, and it is important to supplement the three principal meals by taking a milk drink with chocolate biscuits or bread in the middle of the morning and in the afternoon and last thing at night. All food must be carefully chewed before swallowing.

4. *It is a mistake to avoid certain foods* (with the exceptions mentioned above) on principle because they are supposed to be indigestible. Narrowing the diet down too much leads to a loss of weight and malnutrition, which will tend to cause a recurrence of the indigestion. Eat any food that is available, unless it is found that a certain food always disagrees, in which case it should be avoided.

5. *If constipated* take a teaspoonful of milk of magnesia at night or a dessertspoonful of liquid paraffin morning and evening.

6. *Try to avoid mental and physical overstrain.* Keep regular hours, regular habits, and, above all, regular mealtimes. During unavoidable periods of extra work, intensive activity, or excitement, or when worried or upset, take extra care with diet: avoid beef, pork, pastry, and greasy foods.

7. *If indigestion is felt* take a dose of alkaline powder (magnesium trisilicate if possible), but do not take powder as a routine. Otherwise avoid all medicines, unless ordered by your doctor. If the indigestion is severe and does not clear up in a few days go and see your doctor.

8. Do not spend all your time worrying about your stomach and about your diet and about your health generally. Stick to these instructions, but otherwise forget about your stomach and enjoy life.

The following is a copy of the questionary sent to each of the patients who failed to keep his final follow-up appointment:

"I am very interested to hear how your indigestion has been since I last saw you, as we are doing some investigations on the subject.

"I should be most grateful if you would write to me in confidence (envelope enclosed) telling me in detail about any symptoms you have noticed, and also whether you have had any further treatment or operations, the date and results of any further barium-meal x-ray films of your stomach, and any complications that have occurred.

"Are you keeping to a diet, are you working, and how much tobacco are you smoking?"

During the last quarter of 1953 the City Analyst of Birmingham carried out a survey of five popular brands of "pocket inhaler." These articles consist of a conical plastic outer case with a smaller inner chamber containing absorbent paper soaked in amphetamine, or a closely related compound, together with menthol and essential oils. Sixty-four inhalers were examined, an average of 13 of each of the five brands. The first of these brands to be put on the market showed a remarkably consistent amphetamine content. Three other brands were very similar, but their content of amphetamine was less constant, sometimes showing an excess of up to 30%, and sometimes a deficiency of as much as 22%. The last brand examined, however, presented a very different picture: of 13 samples examined every one was deficient in amphetamine by amounts varying from 31% to 90%, with an average shortage of nearly 60%. The City Analyst then wrote to the makers, who suggested that the loss was due to evaporation consequent on long storage. However, no particular relationship could be discovered between age and the strength of the samples. As a result of this investigation the firm in question agreed to recall all inhalers issued before last year. In Mr. Bagnall's view, this appears to be yet another case where certain pharmacists have retained stocks of a preparation long after the time when they should have been destroyed or returned to the suppliers.

A PLEA FOR THE LONGER TREATMENT OF CHRONIC PYELONEPHRITIS IN CHILDREN

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Acute pyelonephritis in children responds to sulphonamides so well that its treatment rarely presents a problem. Sixteen cases in infants and children were treated in the Radcliffe Infirmary during 1948 and 1949; all cleared up rapidly and only one relapsed. The latter responded to a second course of sulphonamide, and there was no recurrence.

In chronic pyelonephritis the results are very different. In the same two-year period there were 16 chronic cases at the Radcliffe. Symptoms had been present for at least two weeks, and in most cases for very much longer when treatment was started. They were all given a sulphonamide in full dosage for five to fourteen days. In every case the infection relapsed. In four of these cases further investigation showed lesions requiring surgery, but the other 12 remained essentially medical problems. Our experience since then suggests that these results are in no way exceptional, and it is with the treatment of chronic pyelonephritis without surgically treatable lesions that this paper is concerned. In most cases the infection is due to a coliform organism sensitive initially to all the readily available antibiotics except penicillin. The question to be decided is which antibiotic should be used, in what dose, and for how long.

General Considerations

In 1939 Weiss and Parker reviewed the post-mortem findings in 100 cases of chronic renal tract infection. In only one was inflammation confined to the renal pelves and ureters; in 99 inflammation involved the renal parenchyma, and the disease was rightly called pyelonephritis. Birchall and Alexander (1950), in a review of the medical aspects of pyelonephritis, accepted this view of its pathology. They pointed out that in treatment it is the concentration of antibiotic in the plasma which is significant, and not the concentration in the urine. Therefore only full doses of a sulphonamide or antibiotic should be given in the initial treatment of pyelonephritis. Furthermore, there is no particular merit in a sulphonamide such as "urolucosil," which has been recommended because of the high concentration of the non-acetylated form obtained in the urine. Birchall and Alexander also draw attention to the fairly general experience that, with streptomycin, organisms become resistant very rapidly. They suggested, for this reason, that streptomycin should never be given for more than five to seven days. They also pointed out that as mandelic acid and related compounds are effective only in an acid medium, which cannot be attained in the interstitial tissues of the kidney, these drugs are unlikely to be of value in pyelonephritis, and should be reserved for infections of the lower renal tract. For the treatment of chronic pyelonephritis they recommended a 21-days course of a sulphonamide in

full dosage, together with intramuscular penicillin and streptomycin during the first week.

At the time their article was published we had no experience of this combined therapy, but we had already been using 14-days courses of a sulphonamide in full dosage, and had had four quite severe drug reactions. Two children on sulphadimidine developed rashes with generalized lymph-node enlargement on the seventh and eighth days of the course respectively. One child on "sulphatriad" developed fever and a rash on the eleventh day, and another on a rather large dose of sulphatriad—0.15 g. per lb. (0.33 g. per kg.) a day; body weight 20 lb. (9 kg.)—developed on the thirteenth day fever, generalized lymph-node enlargement with splenomegaly, and agranulocytosis with complete disappearance of polymorphs from the peripheral blood for nearly a week. This experience made us reluctant to give even longer courses of sulphonamides in full dosage. Furthermore, we already had, in one child, evidence of the value of a small dose of a sulphonamide continued over a very long period. We therefore decided to start treating all cases of chronic pyelonephritis with an initial 10-days course of sulphadimidine in full dosage, followed by a further variable period on a small dose.

It is clearly important to know whether this method of treatment gives better results than the orthodox short course. Only a planned investigation could give this information with certainty, and no such investigation has been made. However, during the last three and a half years we have treated over 40 infants and young children with chronic pyelonephritis in the Babies' Hospital, Newcastle-upon-Tyne, during the first half of this period with short courses of a sulphonamide or antibiotic, and during the second half with long courses. From among these infants it has been possible to form reasonably similar groups, and a comparison of the results of treatment in the two groups follows.

An Investigation

During this investigation the general management, nursing care, and follow-up of infants remained the same; only the length of treatment changed significantly.

Infants admitted before October, 1950, were treated with sulphadimidine, streptomycin, or chloramphenicol for five to fourteen days, seven days being the most usual. Dosage was standard—that is, sulphadimidine, 0.1 g. per lb. (0.22 g. per kg.) a day; streptomycin, 20 mg. per lb. (44 mg. per kg.) a day; and chloramphenicol, 50 mg. per lb. (110 mg. per kg.) a day. If the infection relapsed, a second similar course of appropriate antibiotic was given, and in some cases third and fourth courses. "Mandelix" was used in three cases after antibiotics had failed. If infection still persisted infants were kept on sodium citrate (average 90 gr. (6 g.) a day) for long periods.

After October, 1950, sulphadimidine was given in full dosage for an initial period, usually 10 days; the subsequent period on a reduced dose varied from only 10 days in two cases to over six months. If the infection did not respond to sulphadimidine or if the organism seemed unlikely to be sensitive—for example, *Staph. aureus*—chloramphenicol was used. Rather illogically, in the first case we treated with chloramphenicol (No. 17) this was given for only 16 days. The infection relapsed. Whenever we used chloramphenicol in subsequent cases we gave an initial course, usually of fourteen days, in full dosage and then a reduced dose for a period varying from six to sixteen weeks. Streptomycin was given in most cases during the first week of sulphadimidine. Alkalis were not used.

Only infants with a indisputable pyelonephritis who were under 1 year at the onset of symptoms, whose symptoms had been present for at least two weeks before the start of treatment, who had no evidence of renal acidosis or of hypercalcaemia, and who had no other illness which might have affected the course of the pyelonephritis have been included for analysis. Twelve infants in the early group and 11 in the later group satisfied these criteria.

The duration of symptoms before treatment is probably the most important single factor in determining prognosis. This was similar in the two groups. The results of treatment proved extremely difficult to assess. It was out of the question to use the urinary findings alone as an index of cure, and we therefore had to depend very much on the infant's general progress. Failure to thrive is so constantly present in infants with an active infection that a normal weight gain is a dependable sign of recovery. All weights were therefore graphed, and these, the mother's account of the infant, and the urinary findings were all taken into consideration. To express the results quantitatively, we tried to decide on a definite day, counting from the start of treatment, from which progress was uninterrupted and after which no significant pyuria was found. This was easy when there was a good immediate response to treatment with no relapse. Although there were minor variations in response, for the sake of clarity all such cases have been graded as 10—that is, progress uninterrupted from the tenth day of treatment. It was still fairly easy in the cases which relapsed but made a good recovery after further treatment, and all these have been given a definite grading. It was impossible in those cases in which, after months of ill-health with slow or fluctuating weight gains, gradual and possibly incomplete recovery occurred: in these no attempt has been made to be precise.

The results of this analysis are given in the Table. There is no doubt that the results of treatment are very much better in the later group. Six of the 11 made an uninterrupted recovery, against 4 out of 12. The average time from the start of treatment to recovery was less than half, and there was only one case with an indefinite end-point against three in the early group. However, in 5 of the 11 cases in the later group recovery was slow and interrupted. In two of these the reasons for this are obscure, but in three it is instructive to examine the treatment given in detail.

Results of Treatment

Early Group			Later Group		
Case No.	Duration of Symptoms in Days before Treatment	Days from Start of Treatment to Recovery	Case No.	Duration of Symptoms in Days before Treatment	Days from Start of Treatment to Recovery
1	210	90	13	? 184	>120
2	182	>150	14	182	10
3	119	10	15	154	10
4	119	10	16	119	51
5	98	10	17	91	90
6	98	60	18	70	10
7	84	200	19	70	10
8	70	10	20	56	78
9	56	>90	21	49	10
10	35	300	22	42	10
11	35	>60	23	28	110
12	17	60			
Average	93·6	$\frac{750}{9}$ = 83·3 plus 3 indefinite	Average	95·0	$\frac{389}{10}$ = 38·9 plus 1 indefinite

Case 17.—This child was in hospital at the same time as several infants with a gastro-enteritis due to *Bact. coli* D 433. He passed some loose stools shortly after admission, and it was because of the possible intercurrent gastro-enteritis that he was treated from the start with chloramphenicol rather than sulphadimidine. He responded well to a 16-days course, but the infection relapsed within a week. The infection then failed to respond to sulphadimidine given for 28 days when he was an out-patient, presumably because the organism was insensitive; so he was readmitted to hospital. A coliform organism sensitive to chloramphenicol was cultured from the urine, and he was given chloramphenicol, 250 mg. four-hourly for 14 days, 250 mg. twice-daily for 42 days, and 250 mg. once daily for 84 days. The infection responded promptly and has not relapsed in over a year's follow-up. He was given this very long course

because a persistently raised blood urea and no visible excretion of dye in an intravenous pyelogram suggested severe kidney damage.

Case 16.—This male child was treated initially with sulphadimidine, 0.25 g. four-hourly for ten days, with streptomycin during the first seven days. This was followed by sulphadimidine, 0.25 g. twice daily for seven days. The pyelonephritis had responded to this, but he then developed an abscess at the site of a streptomycin injection. Pus from this cultured *Staph. aureus* resistant to penicillin and streptomycin. Sulphadimidine was stopped and he was given chloramphenicol, 250 mg. eight-hourly for eight days. Total treatment was for only 25 days: the shortness of this course was due to a mistake, and was not in keeping with the general policy. The pyelonephritis relapsed after one week. His urine cultured coliform organisms still sensitive to chloramphenicol, and he was given chloramphenicol, 250 mg. eight-hourly for 21 days, and 125 mg. twice daily for 56 days. The infection responded promptly to this, and has not relapsed in nine months' follow-up.

Case 20.—A female child was treated initially with sulphadimidine, 0.5 g. six-hourly for 10 days followed by 0.5 g. twice daily for 21 days (total treatment 31 days). The infection responded promptly, but symptoms recurred a week after stopping treatment. They were at first attributed to a mild otitis media, for which penicillin was given for a week, but pyuria was found later. Urine culture revealed a chloramphenicol-sensitive coliform organism, and she was given chloramphenicol, 500 mg. eight-hourly for 14 days, and 250 mg. twice daily for 56 days. The infection responded, and there was no relapse in three months' follow-up.

In these three cases it seems probable that relapse could have been prevented by giving a longer course of treatment on the first occasion.

Conclusion and Discussion

From the evidence of this investigation it is clear that the plan of treatment followed in the later group offers a good chance of cure even in very long-standing infections. If the infection responds to the initial course of sulphadimidine or chloramphenicol in full dosage, relapse is most unlikely during the subsequent period on a reduced dose. We have in fact never seen this. The difficult question is how long the reduced dose should be continued. The results in Cases 16 and 20, which relapsed after 25 and 31 days of treatment respectively, suggest that the period must certainly be longer than a month, but we do not know how often we have used unnecessarily long courses.

It is perhaps worth considering at this point why the long period on a reduced dose prevents relapse. The following explanation seems reasonable. It is certain that in every case of long-standing pyelonephritis there is widespread disorganization of renal tissue. It is unlikely that this damaged tissue can be restored to normal in a period as short as two or three weeks, and while it remains incompletely healed it is presumably more liable to infection. The initial course of antibiotic in full dosage must kill most of the infecting organisms, but a few may survive in isolated foci. We imagine that the small dose of antibiotic is enough to protect the damaged tissue from infection spreading from the surviving foci. As the organism found in relapse is nearly always the same as in the original infection, relapse must usually occur by spread of infection from surviving foci rather than by reinfection with fresh organisms.

If this is the correct explanation the protective dose of antibiotic must be continued for as long as the damaged kidney will take to heal, and this will depend on the duration and severity of the infection before treatment was started. There can therefore be no final answer to this question of how long treatment should be continued. The length of history, the extent to which one or both kidneys have already been damaged, and the possible risk of toxic effects from the long course of antibiotic will all have to be taken into consideration.

Sulphadimidine is so cheap and safe that we are sure it should be used first whenever it is likely to be effective. For the same reasons, wherever the initial course in full dosage has proved effective it would seem wise to anticipate relapse and to give the reduced dose for a long period. As an approximate guide we would suggest eight weeks when infection has been present for less than two months, and up to six months or occasionally more in longer-standing infections.

When we have had to turn to another antibiotic we have used chloramphenicol, and our experience with this suggests that the same manner of dosage is needed as with sulphadimidine. We have used it in this way with good results and without any serious ill effects. However, reports (Hodgkinson, 1954) of aplastic anaemia following chloramphenicol suggest that it would be most unwise to make a practice of giving long courses. A final verdict on this question is not possible yet, but for the present it seems preferable to use aureomycin. It is most unlikely that aureomycin will prove effective in a significantly smaller dose or shorter time than chloramphenicol or sulphadimidine, and our very limited experience confirms this view. However, it is more expensive than sulphadimidine and its long-term toxic effects are less well explored. For both these reasons we are reluctant to advise giving really long courses unless they are absolutely essential. In the great majority of cases we believe they will be, but as a small proportion of cases clear up after a short course of treatment (see Cases 3, 4, 5, and 8) it may be wise to start with a 14-days course. If the infection relapses it is still likely to respond to a longer period of treatment as suggested for sulphadimidine.

Although most of those we have treated for pyelonephritis have been infants, limited experience with older children suggests that our conclusions are valid for them too. In older children, however, histories tend to be longer, and one occasionally meets with infections which are distressingly intractable. In such cases persistent treatment with frequent change of antibiotic as bacteriology indicates offers the only hope of cure.

Summary

All cases of pyelonephritis in infants and young children treated during 1948–9 at the Radcliffe Infirmary, Oxford, and in a 3½-year period (1949–52) at the Babies' Hospital, Newcastle-upon-Tyne, have been studied.

Attention is drawn to the possible chronicity of these infections and to the frequency of relapse after orthodox seven- to fourteen-days courses of a sulphonamide or antibiotic.

A new scheme of treatment has been described with an initial ten-days course of sulphadimidine or an antibiotic in full dosage, followed by a long period (two to six months) on a reduced dose.

Two similar groups of cases—one treated in the orthodox manner and the other according to the new scheme—are compared, and the superiority of the long course of treatment is shown.

The wisest plan of treatment to adopt in future is discussed.

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DEEP X-RAY THERAPY IN SPONDYLITIS

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Since late 1947 a joint clinic has been conducted at the Rheumatism Centre and at the Christie Hospital and Holt Radium Institute for the investigation of cases of ankylosing spondylitis and their treatment by *x* rays. This paper concerns 332 cases seen under this joint arrangement and the changes observed in 275 of these following *x*-ray therapy.

The clinical picture of ankylosing spondylitis has been fully described in several recent publications (Polley and Slocumb, 1947; Mowbray *et al.*, 1949; Parr *et al.*, 1951), and notably in those of Hart *et al.* (1949, 1950). During the course of the present study patients whose disease conformed to the classical picture were labelled "typical" spondylitics, but there were some patients whose illness differed in various ways from this and who were classed as "atypical" spondylitics in the absence of a satisfactory alternative diagnosis. Some of the patients seen in the spondylitis clinic were found on further investigation to be suffering from conditions unrelated to spondylitis, such as bone disease, disk prolapse, and spinal cord lesions, but these have been excluded from this study. During the analysis of the spondylitic cases a "borderline" group was also introduced between the "typical" and "atypical" groups. *X*-ray therapy was not advised in a number of the atypical cases although many had been referred for this, and one of our purposes was to find out if that policy was in fact justified. *X*-ray treatment was also not given to typical cases in which the spondylitis appeared to be inactive.

Of the 332 cases, 242 were considered to be typical, 59 atypical, and 31 borderline. Some of the features of these cases are set out in Table I.

About one-quarter of the patients in each group gave histories of rheumatic complaints among relatives; in the typical group 35% of these were of fairly definite or probable ankylosing spondylitis, compared with 19% in the atypical group, but the difference is not significant ($P>0.16$). The incidence of iritis in the three groups did not differ significantly. The true incidence of involvement of the hands and feet in ankylosing spondylitis may be somewhat higher than is indicated owing to the inclusion of some typical cases in the borderline group, but if these groups are combined the incidence of 34 in 273 cases (12.5%) contrasts with the incidence of 52.5% in the atypical group. Tendinitis and tendon nodules were noted very rarely in typical spondylitics but were found in 12% of the atypical patients. Ball's modification of Rose's serum differential agglutination test (Ball, 1950) gave strongly positive results in 12% of the 50 atypical patients tested. Ball (1952) reported positive results with this test in 44.2% of 642 unselected cases of rheumatoid arthritis attending hospital. This suggests that the atypical group is not largely composed of patients with rheumatoid arthritis affecting the spine in spite of the high incidence among them of involvement of the hands and feet.

TABLE I

	Typical	Borderline	Atypical
Total No. of Cases	242	31	59
Males	197	28	45
Females	45	3	14
Family history:			
Definite ankylosing spondylitis	13	0	3
Probable " "	10	0	0
Miscellaneous rheumatic complaints	43	8	13
Definite history of iritis	19	3	3
Probable " " "	4	1	0
Hands or feet involved	12	22	31
Tendon lesions	2	1	7
Differential agglutination tests	125	22	50
Strongly positive	3	0	6
Weakly or doubtfully positive	4	0	1
Negative	118	22	43
Clinical status:			
Mean disability score* before treatment	6·04±2·24	7·91±1·81	6·4±2·36
" " " after "	3·84±2·16	5·31±2·70	4·92±2·75
Duration of symptoms when treated:			
5 years or less	62	8	14
More than 5 years	150	20	21
X-ray grade:†			
I	43	3	6
II	167	25	41
III	31	0	1
Not known	1	3	2
Sacro-iliac joints normal but change elsewhere	0	0	6
X-ray films normal	0	0	3

* Treated patients only (see text).
† Grade I=Sacro-iliac joints only involved. Grade II=Sacro-iliac joints involved+slight or moderate change in spine or elsewhere. Grade III=Sacro-iliac joints involved+severe and extensive change in spine or elsewhere.

Technique of X-ray Treatment

The *x* rays were generated at 250 kV with a half-value layer of 1.63 mm. of copper, the focus–skin distance being 50 cm. It has been our practice, even when symptoms were confined to one level of the back, to treat the whole spine and the sacro-iliac joints through rectangular applicators 7.5 cm. in width, the length being adjusted so as to ensure close apposition of these to the skin.

Previously, smaller fields were used to treat local painful regions of the spine, but this method was abandoned because, although the treated area might be painless after treatment, further lesions in the vicinity often developed or were disclosed during treatment. The sacro-iliac joints were treated through a single applicator, 15 by 12 cm., contiguous with the lowermost spinal field.

Almost all these patients were treated as out-patients, a dose of 150 r (measured with back-scatter) being given to the skin surface of each field at each weekly visit for ten weeks. Serious radiation sickness occurs infrequently with this low dosage, having caused curtailment of treatment in only four of these patients. It was also hoped that this dosage would decrease the likelihood of haematological complications, particularly in patients requiring retreatment at a later date.

Peripheral joints were treated through parallel opposing fields, a maximum skin dosage of 150 r being delivered to each field weekly for ten weeks. In treatment of the carpus and tarsus, as in the spine, large fields covering the whole of these groups of small joints proved most successful. For the tarsus, fields approximately 25 by 12.5 cm., to include the whole foot and ankle-joint, were used.

Localized painful lesions over bony prominences such as ischial tuberosities, adductor tubercles, and iliac crests, and painful costochondral junctions, were given single exposures through small fields to a dose of 500 or 600 r.

Method of Assessment

For analysis, the patient's status was assessed in terms of constitutional disturbance, pain, range of movement, and general functional capacity. In order to obtain some quan-

titative expression of disability before and after treatment for statistical analysis as a check on the general clinical assessment of the case, the patient was given a numerical score for each of these features, scores of from 0 to 2 being awarded for increasing degrees of constitutional disturbance, of from 0 to 3 for pain of increasing severity, and of from 0 to 3 for increasing impairment of spinal movement. Functional capacity was scored in five grades—from grade 1, in which the patient was fully employed or employable in normal work and able to undertake normal physical recreations for his or her type, to grade 5, in which he was confined to bed unable to look after himself. The total or "disability score" was taken to represent a measure of the patient's disability.

Patients considered to be "much improved" had complete or almost complete freedom from pain after treatment, the associated constitutional disturbance was abolished or significantly decreased, and they usually gained weight. The general functional capacity of the patient was increased, and in cases without extensive radiological changes the range of movement often, but not invariably, improved. Photographic records of the range of back movement done in some cases gave valuable objective evidence of this (Figs. 1 and 2).

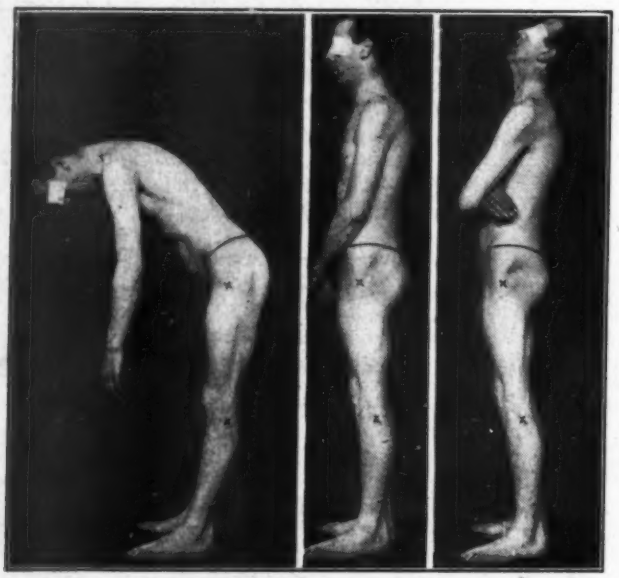

FIG. 1.—Before *x*-ray treatment.

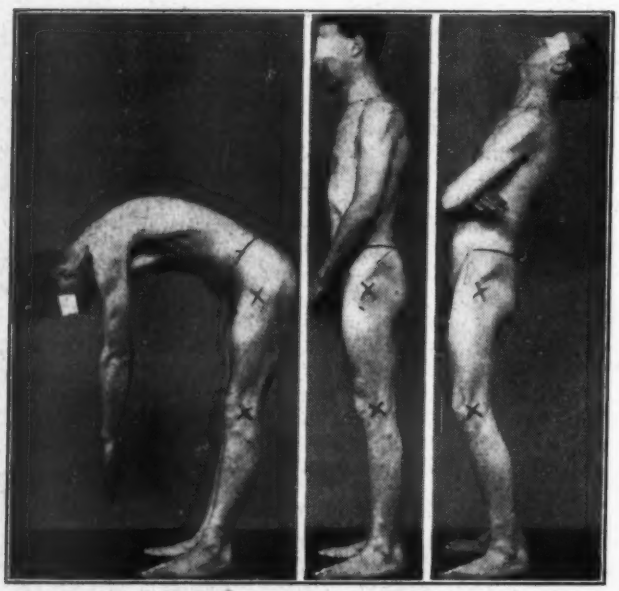

FIG. 2.—Two months after *x*-ray treatment

"Slightly improved" signified less improvement in these respects, usually implying persistence of pain of significant degree in the treated area. A smaller number of cases were included in this category, since, although the treated areas were much improved, the beneficial effect was overshadowed by the development of new lesions elsewhere. Improvement was usually first noted about the middle of the course, and maximum improvement within the first two months or so after treatment, though a few cases continued to improve for about six months.

The patients were assessed before and one month after completion of treatment and at intervals thereafter, in the first instance one year, but before this when necessary. They were in all cases instructed to report to the clinic should relapse occur before their appointments fell due.

Results

The numbers of patients treated in the three groups and their status after treatment are shown in Table II.

TABLE II

	Typical		Borderline		Atypical	
	Male	Female	Male	Female	Male	Female
Total No. of cases ..	197	45	28	3	45	14
No. treated	175	37	26	2	27	8
Much improved after treatment	124	25	16	2	9	2
Slightly improved after treatment	41	10	6	0	9	2
No change after treatment	3	1	2	0	5	3
Unable to assess ..	7	1	2	0	4	1

As the proportions of males and females much improved after treatment do not differ significantly in either the typical or the atypical groups ($P=0.69$ and $=0.64$ respectively) the figures for males and females have been grouped together in the subsequent analysis.

The proportion of patients much improved after treatment is very significantly higher in the typical than in the atypical group ($P<0.00001$). The distributions of the disability scores in the two groups before treatment tested by the χ^2 method do not differ significantly ($P<0.96$), but a highly significant difference in these is apparent after treatment ($P<0.0008$). This difference is due to a significant increase in the proportions of patients in the typical group in the lower disability classes after treatment, whereas in the atypical group the proportions are not significantly altered.

In Table III a further analysis is made of patients in the typical group much improved after treatment.

Elevation of the blood sedimentation rate above 20/200 mm. Westergren is no guide to whether a patient will be improved after *x*-ray therapy. Hart *et al.* (1949) came to a similar conclusion. We recommend *x*-ray treatment only in cases in which the ankylosing spondylitis

TABLE III.—*Analysis of Typical Cases*

	No.	Treated	Much Improved	P
B.S.R. >20/200 mm.	162	141	98	>0·7
,, 20/200 mm. or less ..	68	60	43	
,, not stated	12*			
Peripheral joints:				
Treated concurrently with spine		32	17	>0·6
Treated separately		30	14	
Age < 45 years when treated:				
Duration 5 years or less ..		57	47	<·01
,, >5 years		109	71	
Age 45 years or more when treated:				
Duration 5 years or less ..		5	5	
,, > 5 years		41	26	
Radiological Grade I	43	38	33	<0·01 / 0·38 / <0·01
,, ,, II	167	149	101	
,, ,, III	31	24	14	
,, ,, not known ..	1			

*Eleven of these patients were treated, and eight were considered to be much improved after treatment.

appears "active," as we have been unimpressed by the results of treatment of patients with little pain, either spontaneous or on movement, or constitutional disturbance, though they may have severe limitation of movement and extensive radiological changes typical of the disease. This means that judgment of the "activity" of the disease must be largely based on clinical criteria.

As might be expected, the probability of improvement after treatment is higher in patients whose symptoms are of short duration. That the duration of symptoms rather than the age at which treatment is given is the factor concerned is suggested by the observation that among patients with symptoms of more than five years' duration the proportions much improved after treatment in the age groups above and below 45 years are almost identical. In keeping with this is the finding that significantly fewer patients were much improved after treatment when radiological changes were also present in the spine or elsewhere than when changes were confined to the sacro-iliac joints—a finding similar to that of Smyth *et al.* (1941a). It should be added that no such relationship between duration of symptoms and improvement after treatment can be shown in the atypical group, in which improvement appeared to be related to the age of the patient and unconnected with duration of symptoms, but this impression was not confirmed statistically.

Seventeen patients in the typical group have been given second courses of treatment to previously treated areas, 15 of these to the spine and sacro-iliac joints. Seven of these 17 patients were much improved after treatment, a significantly smaller proportion than after the first course ($P<0.02$).

We do not yet know how long the improvement after treatment will be maintained in most of these patients, but up to February, 1953, 56 of the typical cases had relapsed, and in 44 of these relapses areas treated in the first course were involved.

Thirty-two of the relapsed patients had been regarded as much improved after treatment, and of these none relapsed in the first six months after treatment, whereas five of the slightly improved patients relapsed during this period. Of the seven patients much improved after a second course of treatment, one has so far relapsed in the second six months after its completion; four of these patients have not yet been seen six months after treatment. It is unlikely that many more patients have had major relapses without our learning of these, as relapsed patients have usually been anxious to have further *x*-ray treatment, which in this region is entirely controlled from the Christie Hospital and the Holt Radium Institute.

Complications of X-ray Treatment

These relate to 301 courses of treatment given to 275 individuals. Twenty-five patients received two courses, 21 of these to the spine, and one patient has had three courses to the spine.

The only serious haematological complication encountered was in a man aged 44 whose haemoglobin prior to *x*-ray treatment was 64% (9.5 g. per 100 ml.). After seven weekly treatments to the spine and sacro-iliac joints profuse bleeding occurred from a rectal polyp and he rapidly became severely anaemic, requiring repeated transfusion. Sternal marrow examination revealed an aplastic picture, and no improvement in either the blood count or marrow appearances occurred with A.C.T.H. treatment. His spondylitis was little if any improved after treatment, and he was maintained in indifferent health by regular blood transfusions, to which he showed gradually diminishing response, dying with extensive haemochromatosis two and a half years after treatment.

In one patient inactive pulmonary tuberculosis seemed to be reactivated by treatment to the spine, and on being informed of his extensive pulmonary disease he committed suicide in a fit of depression. Since this occurrence routine radiographs of the chest have been taken before *x*-ray therapy to the spine, and seven other known cases of inactive pulmonary tuberculosis have been treated without complication.

Two other patients have died. One was a woman aged 57 with atypical spondylitis and features of Cushing's syndrome. Hypertension was present before treatment, and after nine weekly treatments to the spine and a single exposure of 600 r to the sternum and sterno-clavicular joints she complained of increasing weakness, tiredness, anorexia, and loss of weight. Albuminuria, azotaemia, and greatly reduced renal function were detected. She died at home in heart failure two months after treatment.

The other was a man aged 39 whose arthritis appeared typical of spondylitis. He had an associated inactive chronic pyelonephritis with hypertension and azotaemia, and, though much improved in respect of his spondylitis after treatment, he died in uraemia eight months later.

It is possible that in both these patients *x*-ray therapy may have accelerated the renal failure, although the radiation dosage to the kidneys in these cases was considerably less than that found to produce permanent renal drainage in man by Kunkler *et al.* (1952).

Permanent amenorrhoea after treatment occurred in 13 of the 47 females treated, and probably also in three further cases; 13 of these were below the age of 45. Temporary amenorrhoea lasting up to one year occurred in three other cases, all below 35. Since this high incidence of post-treatment amenorrhoea was disclosed by analysis of these cases, a tangential field method of treatment of the sacro-iliac joints in females has been adopted. Radiation to the ovaries should be less by this technique, but too few cases have so far been treated to assess how often it results in amenorrhoea.

No other serious complications were noted.

Other Treatment

The patients were encouraged to lead as normal lives as possible within the limits of their disabilities. They were instructed in the performance of breathing exercises and simple measures aimed at correction of deformity, such as sleeping supine on a firm bed and gradually decreasing the number of pillows, and were advised to avoid prolonged stooping and heavy lifting in a flexed position. Some of the more severely disabled patients with potentially correctable deformities were also given a more intensive course of reablement as in-patients of the Devonshire Royal Hospital in Buxton. Eight patients, all with severe bilateral involvement of the hips, were referred for hip surgery, and one was referred for spinal osteotomy.

Immobilization

Spinal supports were rarely advised, as we have not been impressed by their value in preventing spinal deformity or relieving pain due to established deformity, although a number of patients had been provided with such supports before coming to the clinic. Patients were confined to bed only in exceptional circumstances. The few patients who had been immobilized, particularly those in whom the lower limbs and spine had been immobilized in plaster sometimes because of a mistaken diagnosis of tuberculosis, were as a group strikingly more disabled than the rest of the patients. A similar experience was reported by Swaim (1939). Nineteen patients in our typical group had at some stage been immobilized in bed, in plaster, or on frames for periods of months to years; of these, five were virtual statues with rigid dorsal and lumbar spines and fixed or grossly limited hips, and two of them had practically fixed knees. Only six similar cases were encountered among the remaining 223 patients in the group, and there was no indication from the histories of the immobilized patients that as a group they were examples of more severe disease than the rest of the cases. On the contrary, whereas all six of the patients who had not been immobilized had completely fixed cervical spines, in those cases in which only the lower limbs and lower spine had been immobilized neck

movement was full or only slightly impaired, the gross loss of movement being confined to the parts immobilized.

The case histories of the five patients mentioned illustrate this point.

Case Reports

Case 1.—Man aged 24. In January, 1944, at the age of 18 he developed pain in the right buttock and milder pains in the left shortly afterwards. In October, 1945, tubercle bacilli were found in his sputum, and in January, 1947, lobectomy was performed. In 1949 he began to lose ground, pain in the right buttock increased, and the sputum was again found to be positive. In September, 1949, tuberculosis of the right hip was diagnosed and he was immobilized from the upper dorsal region downwards in an abduction frame. On removal from this after one year, the dorsal and lumbar spines were fixed, the hips ankylosed, and the knees and ankles very limited in movement. Neck movement was full apart from slight restriction laterally, and there was a normal range of movement in the upper limbs. The patient subsequently underwent Girdlestone's operation on the right hip with good results.

Case 2.—Man aged 20. In 1943, when 15 years old, he developed fleeting pains in the low back, knees, and left heel, and left-sided sciatica. After unsuccessful treatment with salicylates and physiotherapy, ankylosing spondylitis was diagnosed in December, 1945. At this time the lumbar spine was straightened, dorso-lumbar extension was absent, and other movements were about three-quarters of normal range. Neck movements were full. There was minimal painful limitation of hip movement, all other limb joints being normal. He was immobilized in plaster beds from the upper dorsal region downwards from January to August, 1946, and again from January to November, 1947. At the end of this period the lower dorsal and lumbar spines, both hips, and both knees were fixed. Neck movement was full, and, apart from some limitation of external rotation of the right shoulder and slight fusiform swelling of finger-joints, the upper limbs were normal.

Case 3.—Man aged 42. In 1934, at the age of 27, he developed pain in the buttocks, which persisted in spite of physiotherapy and spread to the low back. In 1943 a plaster spica was applied to the right hip for two to three months, and reapplied for a further six months in 1944. On removal of this, the left-sided pain increased, and in January, 1945, he was immobilized in a Pearson bed and later in an abduction frame, and then for nine months from the head downwards on a plaster bed. Contrary to instructions, he continued to move his neck, though the plaster prevented extension. On removal from the plaster bed his lumbar and dorsal spines were stiff; extension of the neck was absent, but he had a useful range of other neck movements. Both hips were fixed, the knees had a full range, and the upper limbs were normal apart from minimal limitation of the shoulders. He still suffered pain of moderate severity, but by perseverance he regained a little movement in the spine and left hip. Deep *x*-ray therapy to the spine, sacro-iliac joints, and left hip early in 1950 resulted in complete relief of pain, which has been maintained.

Case 4.—Man aged 28. In 1938 at the age of 16 he noted pains in the feet followed shortly by pains in the interscapular region and neck, which spread during the following three years to all levels of the spine and to the hips. He was told nothing could be done, and took to bed for three years. At the end of this time his spine was completely fixed, apart from a trace of cervical movement, and his hips were ankylosed in flexion with severe total flexion deformity. Both shoulders had about half the normal range; the remaining joints appeared unaffected.

Case 5.—Man aged 41. In 1940 at the age of 26 he developed persistent low back pain and his back began to stiffen. After some months he was admitted to hospital and kept in bed for six months. Subsequently he wore a spinal brace for one year; his pain eased during this period. In 1943 the left knee became painful, and after some weeks in bed both legs stiffened, although previously the right knee had been normal. For the next 18 months he remained on traction without any exercises, and at the end of this time the dorsal and lumbar spines were rigid and he had about half the normal range of neck movement. Both hips were ankylosed and the knees severely limited; movement of the upper limbs was normal. Later he was transferred for cup arthroplasty of both hips.

Discussion

Clinicians dealing with large numbers of patients with ankylosing spondylitis are generally agreed that *x*-ray therapy is of some value in this disease (Kahlmeter, 1930; Hare, 1940; Smyth *et al.*, 1941a; Scott, 1942; Hilton, 1943; McWhirter, 1945; Kuhns and Morrison, 1946; Hart *et al.*, 1949; Parr *et al.*, 1951), and at least two controlled trials have confirmed this clinical impression (Smyth *et al.*, 1941b; Desmarais, 1953), but *x*-ray therapy does not completely arrest the ankylosing process. The best long-term results are therefore achieved by combining this with systematic exercises, positioning in bed and at work, and other physical measures designed to retain mobility and prevent or correct deformity.

In Desmarais's trial the effects of various doses of *x* rays and mock therapy were compared in ankylosing spondylitis, rheumatoid arthritis, and osteoarthritis, and it was found that patients with ankylosing spondylitis showed the greatest improvement, those with osteoarthritis derived some benefit, but the course of patients with rheumatoid arthritis was not significantly different from that of untreated controls. The similarity in behaviour after treatment of peripheral joints treated alone and those treated concurrently with the spine in our typical cases favours the view that the beneficial effect of *x* rays in ankylosing spondylitis is due to a local action on irradiated tissues and not to an indirect effect mediated through an endocrine or other mechanism, and that the failure of rheumatoid joints to improve is due to a difference in tissue responsiveness to *x* rays.

The proportion of treated patients with symptoms of over five years' duration is slightly less in the atypical than in the typical group, so that the poor response to treatment in the atypical group cannot be ascribed to longer duration of symptoms, and the similarity of the mean disability scores and the distribution of these scores in the two groups before treatment argue against the results being due to a preponderance of unusually severe cases in the atypical group. The failure of many patients in the atypical group to benefit from *x*-ray therapy may therefore be due to inclusion in this group of a number of other conditions which resemble ankylosing spondylitis clinically but are unaffected by *x*-ray therapy.

Conclusion

The results of this study suggest that only patients suffering from typical ankylosing spondylitis benefit from *x*-ray therapy. It would therefore be desirable to have well-defined clinical and radiological criteria by which typical spondylitis could be distinguished from other conditions which may simulate this disease. Such a differential diagnosis is also desirable, since immobilization usually aggravates typical spondylitis, while it may be helpful in some of the atypical conditions. We are therefore studying the various arthritic conditions which may simulate ankylosing spondylitis with a view to elaborating a satisfactory differential diagnosis.

Summary

On clinical and radiological grounds 332 cases of spondylitis were divided into three groups: 242 "typical" cases conforming to the classical picture of ankylosing spondylitis, 59 cases classed as "atypical" in the absence of a satisfactory alternative diagnosis, and an intermediate group of 31 "borderline" cases. A family history of rheumatic complaints and a history of iritis were found with

equal frequency in the three groups. In spite of a high incidence of involvement of the hands and feet in the atypical group, the comparatively low proportion of patients in this group giving positive results with Ball's modification of Rose's serum differential agglutination test is evidence that the atypical group is not largely composed of patients with rheumatoid arthritis affecting the spine. The adverse effect of prolonged immobilization in typical ankylosing spondylitis is emphasized.

A total of 275 patients received deep *x*-ray therapy; the proportion much improved after this in the typical group was very significantly higher than in the atypical group. In the typical group, the age or sex of the patient and level of the blood sedimentation rate gave no indication of the probability of improvement after therapy; better results were obtained in patients whose symptoms were of five years' duration or less and in whom radiological changes were confined to the sacro-iliac joints. No significant difference was observed in the behaviour of peripheral joints treated alone and those treated concurrently with the spine, suggesting that the effect of deep *x*-ray therapy in ankylosing spondylitis is a local one on irradiated tissues.

Complications of *x*-ray therapy included one case of aplastic anaemia, reactivation of pulmonary tuberculosis in one case, permanent amenorrhoea in 13 of the 47 females treated, and possible acceleration of renal failure in two cases.

Reasons are given for ascribing the poor results from *x*-ray therapy in the atypical group to inclusion of patients with other diseases simulating ankylosing spondylitis.

We are grateful to the many consultants in this region who have allowed us to study their cases during the investigation; to Professor J. H. Kellgren for much advice and helpful criticism; to Dr. Ralston Paterson for provision of facilities for *x*-ray treatment and follow-up of the patients; to Dr. O. Janus, who saw many of these patients originally in the clinic; and to Miss Marion Russell for help with the statistics.

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Bracken Hill House, The Woods, Northwood, Middlesex, the pioneer hostel of B.R.A. Homes Ltd. (under the aegis of the British Rheumatic Association), is now open. It is designed to meet the needs of industrial workers with early and serious rheumatic conditions for whom bed accommodation at hospitals with rheumatic units is unlikely to be available in the near future. All medical services are provided by Mount Vernon Hospital. Industrial medical officers or the patient's family doctor can apply for accommodation. Cost of beds ranges from £4 15s. to £7 7s. Further details may be obtained from either Bracken Hill House or the British Rheumatic Association, 11, Beaumont Street, London, W.1.

CONGENITAL VALVES IN THE POSTERIOR URETHRA

BY

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A valvular formation of mucosal folds in the posterior urethra is the most often encountered example of the group of congenital anomalies which cause urethral obstruction. A full pathological and clinical description of the condition was given by Young, Frontz, and Baldwin in 1919, yet the lesion has never been widely recognized nor has a satisfactory routine for diagnosis and treatment emerged. I have had the opportunity of operating upon 14 of these valve cases, and the present observations are based upon the study of this series, and of the records of 21 further cases in which the diagnosis has been confirmed by post-mortem examination at the Hospital for Sick Children. All but one of the 14 cases have been treated during the past two years, and it may be of interest to record that during the same period eight cases with other forms of congenital urethral obstructions and four cases of bladder-neck obstruction in young children have come under treatment.

Their Origin

In the characteristic form (Young's type 1) a valve is formed on either side of the urethra by a double fold of mucous membrane, the two meeting in the midline sagittal plane of the urethra, leaving only a small channel anteriorly (Fig. 1). The free edges of the valves are continuous above and posteriorly with ridges connected with the verumontanum; below and anteriorly they fade out on the urethral wall at approximately the level of the external sphincter.

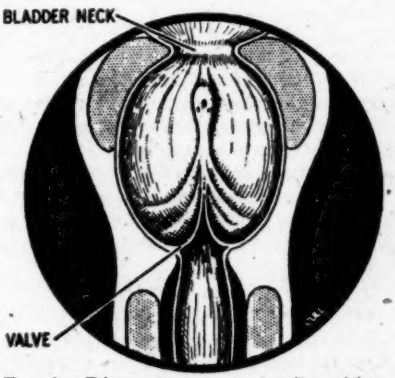

FIG. 1.—Diagram showing the disposition of urethral valves in their most characteristic form. The urethra has been drawn as if it had been opened by a vertical incision of the anterior wall, so that the anterior extremities of the valvular folds are held apart.

Faint ridges with a similar disposition are evident in the normal male urethra, and I have observed that in the embryo they first appear at approximately the 50-mm. stage. The ridges were exceptionally well developed in a 99-mm. embryo which I have examined; they have no discernible function, and after this stage they appear to shrivel spontaneously, but it is clear that it would require only a slight exaggeration of the normal formation with some adhesion of the free edges to bring about the development of an obstructive valve. We are thus dealing with only a minor deviation from the normal, and we should not therefore expect a high instance of multiple congenital anomalies in this disease. In fact, the accompanying abnormalities are chiefly those consequent upon the obstruction.

From this evidence of their origin, it will be manifest that congenital valves will constitute an obstruction to the urinary passages almost from the time that urine is first formed and long before the complete differentiation of the nephrons. A free flow of urine is not, of course, essential

to the general development of the foetus, and growth can proceed almost normally in the complete absence of kidneys; nevertheless, despite conflicting views, it does seem that urine secretion is a normal foetal activity and that urinary obstruction produces hypertrophy of the detrusor, sacculation of the bladder wall, dilatation of the ureters, and hydronephrosis whether it occurs in the foetus or in old age. The urinary tracts of infants dying from this disease during the first few days of life show all the changes associated with long-standing retention of urine, but it is characteristic of the very early obstructions that they cause relatively less bladder distension with relatively greater dilatation of the ureters, and that differentiation of the nephrons is interfered with so that the cortex of the kidney may contain cysts which show no evident connexion with the renal pelvis.

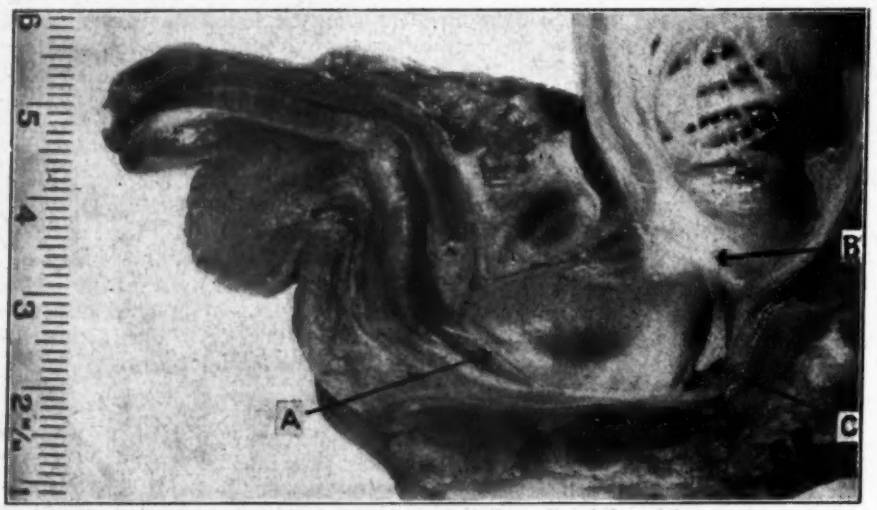

FIG. 2.—Sagittal section through the bladder and urethra of an infant dying on the third day of life (from the Museum of the Hospital for Sick Children, Great Ormond Street). The enormous dilatation of the posterior urethra is clearly shown, and there is a well-marked valvular fold. A, valve; B, bladder neck; C, verumontanum.

These observations apply to all types of congenital infravesical obstruction, but the situation of the valves leads to certain peculiar features. The posterior urethra becomes dilated and considerably elongated (Fig. 2), but the bladder neck remains as a well-defined constriction until a very late stage. The internal sphincter is essentially a condensation of detrusor muscle fibres, and it appears that a general hypertrophy of the bladder muscle must be inevitably associated with bladder-neck hypertrophy.

Clinical Features

On the clinical side, urethral valves present either because of disorders of micturition—incontinence, frequency, haematuria—or because of a deterioration of renal function—failure to thrive, dwarfism, or renal rickets.

Valves scarcely ever cause acute retention. Some urine is always able to dribble away, even though the rapidity of onset of bladder distension may have been sufficient to cause pain. Failure to pass urine during the first few days of postnatal existence is, of course, usually due to dehydration and oliguria, but if the bladder is found distended it is much more likely that the obstruction is an obliteration of the urethra rather than a valve. Overflow incontinence is in fact the most characteristic disturbance of micturition: urine is never passed in a good stream, but the frequent and difficult passage of small quantities or a continuous dribbling makes the child always wet. An infant who is found never to be dry has always some organic disease, and if we can be sure of the truth of this history a most careful investigation is imperative. In older children the incontinence is less easily distinguishable from functional enuresis, though it is usually diurnal as well as nocturnal, and its tendency is to become progressively more severe.

The onset of infection leads to an exacerbation of the obstruction and in the presence of already damaged kidneys may prove overwhelming. The newer sulphonamides and antibiotics can, however, sometimes sterilize the urine even in the presence of an obstruction, and the rapid amelioration of symptoms may then suggest that no further investigation is required. In two of my cases the bladder and kidneys had been palpably distended during an episode of urinary infection at the ages of 1 month and 2 years respectively, yet because apparently normal micturition was re-established after sterilization of the urine the clinician in charge had felt that no organic obstruction could be present. As a result the children were left, one for three months, the other for seven years, before receiving surgical treatment, and in the latter irreparable renal damage had occurred.

Valvular obstruction is for the most part a slowly progressive disorder; sometimes, as in prostatic disease, there is an exacerbation of obstruction for no very obvious reason, and in such cases pain may be a feature. One of my cases was sent to hospital as a possible case of intussusception, and another, who had a large diverticulum, suffered abdominal pain before micturition.

Renal failure manifests itself in a variety of ways, and it is a curious fact that the cases with the most severe signs are often those with comparatively minor disturbances of micturition. During the first few weeks of life vomiting is much the most common presenting sign, and the infant is often suspected of pyloric stenosis until examination reveals distension of the bladder and a continuous dribble of urine. In later infancy and childhood general ill-health and susceptibility to infection or dwarfism may lead to investigation of renal function. Hypovitaminosis-D rickets is now such a rare disease in this country that the presence of a rachitic deformity must always suggest the need for urological investigation.

Diagnosis

Often the observation of an overdistended bladder and of a dribbling incontinence leaves little doubt concerning the presence of a urinary obstruction, and in a few cases the rectal palpation of a full posterior urethra gives assistance in locating the lesion, but the exact diagnosis of urethral valves can never be made on purely clinical grounds. Certain other causes of chronic bladder distension may, of course, be eliminated by clinical examination: the neurological disorders, for instance, are almost invariably accompanied by a recognizable spinal lesion, by sacral anaesthesia, and by paralysis of the anal sphincter. A meatal stenosis, or occasionally a diverticulum of the anterior urethra, may be seen on examination of the penis, but there remain many other obstructive lesions which can be identified only by radiological and endoscopic methods. Recently encountered examples of such lesions include a congenital stenosis of the membranous urethra, a diaphragmatic obstruction above the verumontanum, a duplication of the anterior urethra, and a ureterocele prolapsing through the bladder neck. Bladder-neck obstruction (Marion's disease) is perhaps the disorder most likely to cause confusion, particularly since hypertrophy of the bladder-neck muscle is the usual concomitant of any congenital obstruction lower down the urethra. This difficulty is illustrated by the following case.

A boy of 3½ years was transferred from an orthopaedic hospital, where he had been receiving treatment for a suspected tuberculous lesion of the left femoral neck. He was immobilized on a frame, with traction on the left leg, and a wide-bore needle had been inserted suprapubically to drain a chronically distended bladder.

His blood urea was 68 mg. per 100 ml. and an intravenous pyelogram showed no shadow in either renal area. His position on the frame rendered endoscopy impossible, and the replacement of the needle by some more satisfactory form of drainage seemed imperative. In performing the cystostomy, however, I palpated the bladder neck, which was clearly hypertrophied and resisted dilatation. A generous wedge of tissue was therefore resected from the posterior lip upon the tentative diagnosis of Marion's disease, but I was disappointed to find that no improvement resulted from this operation and that micturition was not re-established. In the meantime, the child had been seen by Mr. E. I. Lloyd, who gave his opinion that the bone lesion was not tuberculous, and that immobilization was not required. A urethroscopy could therefore be undertaken and valvular folds below the verumontanum were then clearly identified. A retropubic valvulotomy was performed and the child subsequently recovered normal micturition without residual urine. A year later the blood urea was 38 mg. per 100 ml. and the pyelogram demonstrated a satisfactory recovery of renal function although some dilatation of the upper urinary tract remained.

FIG. 3.—Micturating cystogram in a boy of 8 years with a palpably distended bladder and incontinence of urine by day and night since age of 5. The dilated posterior urethra is evident; urethroscopy confirmed the presence of urethral valves. Treated by endoscopic resection with satisfactory results.

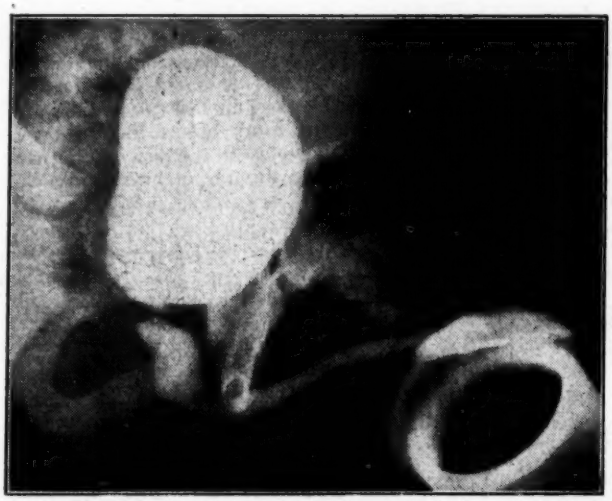

FIG. 4.—Micturating cystogram (oblique view) in a boy of 7 with lifelong dribbling incontinence of urine. Residual urine 6 oz. (170 ml.). Endoscopic resection has eliminated the residual urine and he is now continent.

The most important radiological investigation is the micturating cystogram. A catheter is passed, and the residual urine is drawn off and replaced by a rather larger volume of a 15% diodone solution. The catheter is then withdrawn and exposures are made during micturition (Figs. 3 and 4). These films may show trabeculation of the bladder, the presence of vesical diverticula, reflux into dilated ureters, and dilatation and elongation of the posterior urethra. It should be noticed that unless micturition is actually taking place the urethra may be shut off from the bladder by the hypertrophied internal sphincter, so that it is either not filled at all or contains only a trickle of opaque fluid, giving no true idea of its dimensions. In the young baby in whom micturition is not possible, manual expression of the bladder contents under anaesthesia is often an adequate substitute, but this does not hold good for the older children (Fig. 5). The cysto-urethrogram shows the exact site of the obstruction, and occasionally the actual outline of the valvular folds can be seen, but often the differentiation of the valves from congenital stenosis is impossible.

Cystoscopy and urethroscopy give more detailed information but require special instruments and much more experience for their interpretation. In the infant the instruments must be introduced via a perineal urethrostomy, but, provided this is performed, no particular difficulty should be encountered. I have recently urethroscoped a male infant of 10 days in this way. The cystoscope alone will reveal trabeculation of the bladder and the presence or absence of diverticula. The urethroscope, and preferably one which gives a view directly ahead, is required to identify the nature of the obstruction.

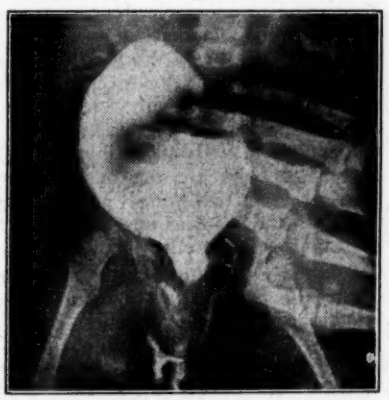

FIG. 5.—Expression cystogram in a boy of 10 months with a blood urea of 212 mg. per 100 ml. Dilatation of the posterior urethra is clearly present, but urethroscopy showed only a congenital stenosis of the membranous region, and there has been a steady improvement, with continuing fall of blood urea, on intermittent dilatation.

Management

The problems encountered in management vary according to the manifestation of the disease. In the infant with a palpably distended bladder, dribbling micturition, and a degree of renal failure, an operation for relief of urinary obstruction will clearly be required, but considerable caution must be exercised in preparing for this operation. It should be realized that drainage of the bladder is not the most urgent need in such a case; the dangers to life are from supervening infection and from a sudden biochemical disturbance, both of which may in fact be precipitated by catheterization. As in the elderly prostatic, the catheter, even when passed with stringent asepsis, may introduce an infection which initiates a rapidly fatal pyelonephritis. Particularly is it dangerous to empty a chronically distended bladder and then allow it to fill up again with a large residual urine. A clear idea of the degree of renal failure and of the presence or absence of other biochemical disturbances is the first essential. The blood urea is the most helpful single investigation, but deceptively high values may be observed if the child is dehydrated, and the estimation should be repeated after adequate fluid has been given.

The range of specific gravity of the urine often gives a useful indication of renal function; commonly the kidneys in severe cases are only capable of producing urine with a specific gravity of 1001 to 1006. Estimations of the bicarbonates, chlorides, sodium, and potassium are important in regulating the fluid and electrolyte requirements, and in long-standing cases with bone changes calcium and phosphorus studies are also required. Once instrumentation has been resorted to, adequate drainage of the urinary tract must be established and, if possible, a definitive treatment carried out. My present routine in such a case is therefore to perform a cystogram and a urethroscopy under anaesthesia, and then, unless the general condition of the child renders it dangerous, to proceed at once to operative removal of the

valve, leaving in a perineal urethrostomy catheter as drainage. In small children an indwelling urethral catheter is scarcely ever an adequate form of drainage: even apart from the danger of stricture formation in the penile urethra, the lumen of the catheter is so small that it easily becomes obstructed.

In the older child who is being investigated for incontinence but who has no serious renal damage, micturating cystography may safely be performed without preparations for immediate operation, provided prophylactic chemotherapy is employed, and full biochemical study may be omitted. The difficulty here is often to know which incontinent boys to investigate, since there is no infallible rule by which they can be segregated. Children with a palpable bladder, those with a continual dribbling incontinence, and older boys who are wet by day as well as by night will clearly be selected, but all enuretics who show no improvement after a fair trial on ordinary treatment should at least be submitted to urethroscopy.

Routine micturating cystography may also be performed during the investigation of recurrent or mild chronic urinary infection. An acute infection complicating an obstruction requires the immediate administration of an antibiotic, and it has seemed wise to give streptomycin while awaiting the bacteriologist's assessment of the susceptibility of the organism. Should there be no response to the antibiotic and if the blood urea is considerably raised, drainage of the urinary tract must be established without delay, and for this purpose a bilateral nephrostomy is far more effective than a suprapubic cystostomy which does not satisfactorily empty the dilated and tortuous ureters.

Operation

Regarding the technique of operation, I believe that the old method of attempting to rupture the valves by passing instruments downwards from the bladder should be discarded: it involves an open bladder, it allows no opportunity for confirmation of the diagnosis, and, as shown by post-mortem examination, often fails in its purpose of destroying the valves. The retropubic operation, in which the urethra is opened by a vertical incision prolonged downwards from the bladder neck to a point well below the verumontanum, can give a beautiful exposure and allows a deliberate surgical removal of the valvular fold, but it is often a prolonged and always a major procedure, it may involve considerable blood loss, and it is a severe tax on a uraemic child. In four cases I have employed an approach through the perineum: the bulb of the urethra is opened up through a longitudinal incision, the membranous region dilated up, and a miniature gorget inserted anteriorly. Then with a flat retractor posteriorly, a sucker, and a headlight the operator is able to get a view of the verumontanum and the valves coming down from it. They can be picked up with a blunt hook and burnt off with the diathermy.

Endoscopic resection, however, constitutes the most satisfactory approach employed so far. The instrument which I have used is an infant version of a simple McCarthy diathermy loop resectoscope, and with it the valvular folds can be scooped off the urethral walls. This type of operation is a comparatively minor procedure which does not place any serious strain on the child, but of course it is never a negligible matter to operate on a case of chronic retention, and the use of the resectoscope must always involve some risk of perforating the urethra, which would lead to a dangerous extravasation of urine, or of damaging the external sphincter and causing permanent incontinence.

Discussion

In discussing the results and complications of the treatment of urethral valves it must again be emphasized that the majority of these children are suffering from long-standing urinary obstruction with severe renal damage. Indeed, those which present during the first month after birth have scarcely ever sufficient functioning renal tissue for survival. In borderline cases it is too often the surgical intervention which precipitates a rapid deterioration of renal function, either through the introduction of infection or through some other mechanism which we do not understand. Post-operative dehydration is always a danger, since the damaged kidneys put out urine of very low specific gravity and require a large volume of fluid in order to excrete the necessary load of solute.

In one case of congenital obstruction, not in fact a valve, an operation which successfully restored normal micturition was followed some weeks later by the development of a severe renal electrolyte loss of sodium and potassium—a type of salt-losing nephritis—which was ultimately the cause of death. One neonatal case of retention had on admission a biochemical pattern resembling Addison's disease, and it could not be determined for certain whether a renal or an adrenal cause was responsible. Another patient, in whom the electrolyte losses had been carefully followed and found normal, died unexpectedly on the third day with cerebral oedema but without any obvious precipitating cause. The biochemical problems involved in treating the obstructive uropathies are therefore complex and as yet poorly understood. It is in this sphere that we hope to make further progress in the future.

Just as the removal of the obstruction cannot lead to an immediate recovery of renal function because of irreversible changes in the kidneys, so too the urinary passages cannot at once regain their normal function. The ureters are tortuous and elongated, and cannot contract down to their former dimensions; in some cases the kinks and adhesions lead to obstruction in the ureter itself, and in several cases drainage of a dilated and obstructed ureter, or nephro-ureterectomy, has been required after the operation for relief of urethral obstruction. The bladder may be atonic, so that it is unable to empty without residuum even after an otherwise successful operation, and if free reflux into the dilated ureters has been established the bladder contractions will serve to fill these ureters rather than to expel the urine. Thus after micturition urine again flows down into the bladder, and catheterization will demonstrate the presence of an apparently large residuum. The loss of normal sensation in the chronically overdistended bladder is also a troublesome feature, since the child does not notice the filling of his bladder and urine may actually be leaking away before micturition is attempted. This is a matter which is capable of improvement by training, however, and should not be a permanent handicap.

Case	Age	Blood Urea (mg./100 ml.)	Operation	Result
1	19 days	66	Cystotomy and passage of sounds from above	Died next day. Grossly diminished renal parenchyma
2	1½ months	53	Retropubic valvulotomy	Satisfactory recovery from operation, but died of jaundice on 19th day
3	3½ ,,	74	Perineal valvulotomy and diverticulectomy	Well one year after operation, but blood urea remains at 66 mg./100 ml.
4	4 ,,	94	Perineal valvulotomy	Died on 7th day with multiple abscesses in kidney
5	4 ,,	86	Retropubic valvulotomy	Died on 2nd day—mongol
6	4½ ,,	51	Perineal valvulotomy and right nephrectomy	Well one year later
7	2½ years	134	Endoscopic resection	Died on 3rd day—oliguria
8	3 ,,	162	Retropubic valvulotomy	Died on 2nd day—oliguria
9	3 ,,	67	Endoscopic resection	Well 3 months later
10	3½ ,,	63	Retropubic valvulotomy	,, 1 year ,,
11	7 ,,	26	Endoscopic resection	,, 6 months ,,
12	8 ,,	41	,, ,,	,, 3 ,, ,,
13	9 ,,	40	Perineal valvulotomy and diverticulectomy	,, 9 ,, ,,
14	11 ,,	150	Bilateral nephrostomy and endoscopic resection	Improved, but residual urine still present. Recent case

The Table summarizes the 14 cases of urethral valves which have been operated upon: clearly, the results leave a great deal to be desired. The older children are much more likely to survive than the infants, but this merely indicates that the older children are suffering from a less severe obstruction and in no way contradicts the view that earlier diagnosis will lead to improved results. More careful attention to the urinary abnormalities of the "under-threes" is required if a significant proportion of children with this disease are to grow up to be healthy adults.

ADDENDUM.—In the eight months which have elapsed since this paper was completed the survivors in the series reported have continued to thrive and five additional cases have been treated. Of these, two, aged 9 days and 11 weeks, died of renal failure before operative treatment of the obstruction had been completed; three, aged 3 weeks, 9 months, and 6 years, have made a satisfactory recovery.

My thanks are due to Mr. Twistington Higgins and to other members of the staff of the Hospital for Sick Children, Great Ormond Street, for allowing me to treat their cases, and to Mr. N. Stidolph, of the Whittington Hospital, for inviting me to see the last of the series. Thanks are also due to Mr. Derek Martin and Mr. P. Cull for their assistance with the illustrations.

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CONTINUOUS CAUDAL ANALGESIA

EXPERIENCES IN THE MANAGEMENT OF DISORDERED UTERINE FUNCTION IN LABOUR*

BY

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Prolonged labour which results from incoordinate action of the uterus or cervix is a serious problem which confronts every obstetrician from time to time. The occasional grave consequences to both mother and foetus have resulted in an increasing tendency to terminate such labours by caesarean section when vaginal delivery is delayed after 36 to 48 hours of established labour (Munro Kerr and Chassar Moir, 1949).

The purpose of this paper is to record the experience gained from the therapeutic application of continuous caudal analgesia to the management of this problem. The comments and conclusions are based on a study of 74 cases of discoordinated action of the uterus or cervix which had prolonged the first stage of labour beyond 48 hours. The clinical types treated included hypotonic inertia, hypertonic lower uterine segment inertia, and primary cervical dystocia (Jeffcoate, 1950). The material has been collected from the Department of Obstetrics and Gynaecology at Newcastle-upon-Tyne General Hospital during the past three and a half years, and 22 cases of cervical dystocia reported in a previous publication (Arthur and Johnson, 1952) are included.

Caudal analgesia was originally devised for minor pelvic operations and described simultaneously by Sicard (1901) and Cathelin (1901). The method is therefore not a new one, but Hingson and Edwards (1943) are largely responsible for describing the modern continuous technique and for applying it to obstetric practice, chiefly as a pain-relieving measure. The intrinsic difficulties and possible complications of the method, in its present form, however, prejudice its widespread adoption for obstetric analgesia, especially when adequate results are obtainable by simpler means. On the other hand, the satisfactory results achieved by its therapeutic use in the management of disordered uterine function justify a wider trial (Nixon, 1952).

The principle of caudal analgesia in the labouring patient is to block the sacral plexus with a suitable local analgesic agent as it lies within the confines of the sacral canal, and to extend the level of analgesia upwards in the extradural space to the level of the tenth dorsal segment.

By this means both the motor and the sensory connexions to the pelvic floor and perineum arising from the sacral plexus are effectively blocked, together with the visceromotor parasympathetic connexions to the cervix. The upward extension of analgesia to the tenth dorsal segment in the extradural space interrupts the sensory connexions to the fundus uteri which enter the cord at this level, and the uterine action becomes painless. The sympathetic visceromotor fibres of the fundus uteri arising from the cord higher up, in the region of the fifth dorsal segment, are uninfluenced by caudal analgesia, while the opposing parasympathetic fibres from the sacral plexus below are paralysed.

Successful caudal analgesia in the labouring patient is therefore aimed at securing unopposed and painless contractions of the uterine fundus, acting upon a completely paralysed and insensitive cervix and birth canal. These conditions seem very suitable for dealing with the problem of either inert uterine function or cervical dystocia, or a combination of these two conditions, and the principle has been adopted in the management of the labours described below.

Methods Used

The technique of continuous caudal analgesia used in this series closely followed that described by Hingson and Edwards (1943). With the patient lying in the left lateral position, a malleable caudal needle was introduced into the sacral canal and connected by a length of fine pressure-tubing, with a 10-ml. syringe and two-way tap interposed, to a bottle of 1.5% piperocaine hydrochloride ("metycaine") in Ringer–Locke solution. The malleable-needle technique was adopted in preference to the indwelling-catheter method for several reasons. In the first place, suitable nylon catheters were not easily obtained, and complications have been reported from time to time with "polythene" catheters. The risk of introducing infection seemed greater with any catheter technique, together with the added risk of tubing fracture. Furthermore, it is doubtful whether polythene catheters can be sterilized with sufficient certainty to insert into the extradural space with complete safety.

The malleable-needle technique proved completely satisfactory, and the requisite apparatus can now be obtained from Messrs. Thackray, Ltd. It was always ready for use, being autoclaved in a small drum together with the necessary drapings.

Analgesia was induced when labour had been prolonged beyond 48 hours owing either to an intrinsic failure of uterine function or to cervical dystocia without any evidence of cephalo-pelvic disproportion.

A preliminary vaginal examination was always made before caudal analgesia, to assess carefully the stage to which labour had progressed and to ensure that the cervix had reached at least one-third dilatation. Hingson and Edwards state that this degree of dilatation is essential, and failure to observe this rule may result in the inhibition of uterine contractions. It is also emphasized that this method

*Condensed from a paper presented to the Newcastle-upon-Tyne Obstetric Society on December 5, 1952.

should not be contemplated if there is any evidence of cephalo-pelvic disproportion, or non-engagement of the head from any other cause whatsoever, for fear of dangerously overdistending a paralysed lower uterine segment.

An initial dose of 40 ml. of piperocaine, injected down the pressure-tubing described above, gave satisfactory analgesia to the tenth dorsal segment for approximately one and a half hours. Thereafter, maintenance doses of 15 ml. were administered at half-hourly intervals. These injections were given by a midwife specially trained in the technique, and the patient was turned on to her opposite side via the abdomen after each half-hourly dose to maintain a bilateral effect. The blood pressure was recorded after each injection, and 20 mg. of methylamphetamine hydrochloride was administered intramuscularly at the onset of caudal analgesia to prevent any severe fall in blood pressure. Analgesia was maintained for approximately six hours in each case, and was then followed by a second vaginal examination to assess progress in cervical dilatation. The subsequent management of each individual case depended upon the progress made.

The comparative findings of the two vaginal examinations enabled each patient to be placed in one of three categories. Group 1 included all those with fully dilated cervices who were immediately delivered with forceps. Group 2 comprised those patients who showed definite progress, but who had not achieved complete dilatation of the cervix after six hours of caudal analgesia. Treatment was continued with half-hourly injections of piperocaine in the confident anticipation of complete dilatation of the cervix, which was achieved in an average of nine hours in all the cases in this second group. The longest caudal block lasted fourteen hours. Group 3 included those who failed to respond at all after the six hours, and delivery was completed by a lower uterine caesarean section without further delay.

Results

The results in the 74 patients subjected to the treatment are given in Table I.

Group 1.—Forty-five patients were found to have completely dilated cervices when the second vaginal examination was performed after four to six hours of treatment. Twenty-seven required simple outlet forceps to complete delivery, the foetal skull lying in the pelvic outlet and the occiput anterior. Sixteen required anterior rotation of the occiput in the mid-cavity of the pelvis from a transverse or posterior position before forceps delivery was completed. The two remaining patients were delivered by breech extraction. There was one stillbirth from an intracranial injury following a difficult breech extraction, and one infant died on the fourth day from pneumonia. In this latter case the membranes had been ruptured surgically for severe pre-eclamptic toxaemia arising two weeks before term. The blood pressure was 210/120 at the time of the rupture of the membranes, and the urine contained 5 g. of albumin per litre.

TABLE I

	Group 1 (45 Cases)			Group 2 (19 Cases)			Group 3 (10 Cases)
	Low Forceps	Anterior Rotation and Forceps	Breech Extraction	Low Forceps	Anterior Rotation and Forceps	Normal Delivery	Lower Segment Caesarean Section
Method of delivery	27	16	2	9	9	1	10
Stillbirths and neonatal deaths	1	0	1	0	0	0	1

Group 2.—Nineteen patients showed progressing but incomplete dilatation of the cervix when the second vaginal examination was carried out after six hours of treatment. Analgesia was continued until full dilatation of the cervix was reached. This was achieved in an average of nine hours, the longest duration being fourteen hours. Nine patients were delivered by a simple outlet forceps with an anteriorly presenting occiput, and nine more required anterior correction of the occiput before forceps delivery was completed. One patient delivered herself spontaneously. There was no stillbirth or neonatal death in any patient included in this second group.

Group 3.—Ten patients showed no further cervical dilatation after six hours of caudal analgesia, and all these were selected for lower uterine caesarean section and delivered successfully. One infant was delivered in a state of white asphyxia and died within a few minutes of delivery, but the remainder survived and did well. This death is attributed to an error of judgment, for caudal analgesia had been unwisely employed when the head remained above the pelvic brim from partial extension of an occipito-posterior position. A strong contraction ring developed in the uterus, and the infant presumably died from partial obstruction of the placental circulation. This case occurred early in the series and served to emphasize further the importance of avoiding caudal analgesia when the greatest diameter of the foetal skull still remains above the pelvic brim.

Table II shows, by comparison with other published data, that in the present series of 74 cases there was no increased incidence of prolonged labour—that is, labour exceeding 48 hours—despite a local interest in this problem.

TABLE II

	Total Labours Exceeding 48 Hours	Stillbirths and Neonatal Deaths		Maternal Deaths		Average Duration of Labour	
		N.-C. Group	Caudal Group	N.-C. Group	Caudal Group	N.-C. Group	Caudal Group
Newcastle General Hospital, 6,957 deliveries	241 (3·4%)	19 (11·4%)	3 (4·1%)	2	0	66·5 hours	58 hours
Queen Charlotte's Hospital, 20,000 deliveries	631 (3·1%)	77 (12%)	—	3	—	74·9 hours	

N.-C. = Non-caudal.

Discussion

The number of patients selected for the treatment gradually increased as technical ability improved and confidence in the method developed. Failures of technique were frequent in the early stages, but, with increasing experience, types of patients—for example, the obese or uncooperative—who had previously been regarded as unsuitable subjects were successfully treated. My recent experience agreed with Hingson's statement that successful caudal analgesia could be achieved in approximately 80% of cases attempted, and the presence of a pilonidal sinus or local sepsis became the main contraindication to the method.

To judge from the results obtained so far, there was a great improvement in the foetal salvage rate in the 74 cases studied. This was doubtless attributable to the overall diminution in the length of labour as shown in the last column of Table II, but a noteworthy observation in the series was the surprising lively condition of the infants at birth (with the exception of the three cases quoted above) despite unmistakable evidence of foetal distress in no fewer than 29 cases before analgesia was started. A suggested explanation of this phenomenon, which is under further investigation, is the dilatation of the uterine arterioles, which might result from blocking their autonomic connexions, thus enhancing the maternal blood supply to the placenta.

Conclusions

The application of continuous caudal analgesia to the management of prolonged labour which resulted from primary failure of uterine function or cervical dystocia has

proved a most valuable addition to the obstetrician's armamentarium.

In many cases the method resulted in speedy dilatation of the cervix to permit earlier delivery of the patient than might have otherwise been expected. Patients showing no response whatever to the treatment were selected for lower segment caesarean section, which was performed on patients who were refreshed by a respite from labour pains. It was deduced from the results obtained that caudal analgesia should be tried when caesarean section might otherwise be seriously regarded as the only satisfactory solution to prolonged and non-progressive labour. By its use many patients will be spared abdominal operation, but, on the other hand, if by failure of response caesarean section is subsequently thought to be necessary, its successful outcome will not have been prejudiced by the previous management.

There were no serious untoward sequelae attributable to caudal analgesia, and this series concludes a pilot study before a more careful statistical investigation is undertaken into the value of the method described in the management of labour exceeding 48 hours.

Summary

The results obtained by employing continuous caudal analgesia as a therapeutic measure in the management of 74 cases of uterine inertia and cervical dystocia, or a combination of these two conditions, are described.

Sixty-four patients were successfully delivered vaginally, with two neonatal deaths, after a period of analgesia lasting from four to fourteen hours.

Ten patients showed no further progress whatever after six hours of caudal analgesia, and were delivered by a lower segment caesarean section.

Continuous caudal analgesia accelerated the progress of labour in a high proportion of cases, and considerably diminished the foetal hazards of this perplexing obstetric problem.

My thanks are due to the nursing staff for preparing the apparatus and managing the patients, and to those obstetricians who have given caudal analgesia a fair chance to see what it can achieve. I am also indebted to Mr. Linton Snaith for his permission to publish the clinical data, and to Professor Harvey Evers and Mr. Hugh Arthur for much helpful criticism and advice in the preparation of this report.

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Medical Memorandum

Supernumerary Pectineus Bursa Causing Femoral Vein Compression

Supernumerary pectineus bursa is a rarity. In the following case recurrent attacks of bursitis had led to femoral vein compression with consequent swelling of the affected leg.

CASE REPORT

A housewife aged 41 was referred to the out-patient department on December 31, 1951, complaining of severe pain in the right thigh which had kept her awake for one night. Her doctor stated that the thigh was greatly swollen and had made a diagnosis of possible venous thrombosis. Two months earlier she had complained only of swelling of the right thigh; there was no pain or tenderness, or any suggestion of a deep vein thrombosis, nor were any inflammatory changes seen in the limb. The doctor thought it was possibly a case of angioneurotic oedema.

On examination her general condition was good. No abnormality was found in the respiratory system, cardiovascular system, or abdomen. The circumference of the right thigh was 2 in. (5 cm.) greater than the left, and the right calf 1 in. (2.5 cm.) greater than the left. There was, however, no evidence of actual oedema. The pulses of the two legs were equal and good. No pelvic abnormality was found on rectal or vaginal examination. There were no varicose veins. *X*-ray examination of the chest, pelvis, lumbar spine, and femora showed nothing abnormal. No cause could be found for this swelling in the limb and she was asked to report again should she get any further attacks, so that she could be seen during an attack.

She reported back on June 17, 1952, stating that during the previous week a lump the size of a walnut had appeared in the right groin. It had been present for two days and had then disappeared. On examination there was no sign of the lump in the groin, and in view of this she was again asked to attend when the lump reappeared.

Her third attendance, on September 22, 1952, showed a swelling the size of a walnut in the right groin situated below and lateral to the pubic spine. It was cystic and tender; the skin was mobile over it, but the swelling was fixed to the underlying muscle. An irreducible femoral hernia was diagnosed and operation undertaken.

At operation by a Lotheissen approach, dissection below the inguinal ligament revealed a cystic swelling which was found to be lying on the pectineus fascia and intimately adherent to the femoral vein. It was realized that this was not a femoral hernia but a bursa arising from the pectineus fascia. It was excised with the exception of a small portion adherent to the femoral vein.

Pathological Report.—The bursa contained gelatinous fluid and had a smooth lining. On histological examination the material was shown to consist of oedematous and congested fibro-vascular tissue, moderately infiltrated with chronic inflammatory cells, eosinophils predominating. In one edge the material was lined by flattened endothelial cells.

The patient made an uneventful convalescence, and on discharge from hospital on October 7 there was no significant difference in the circumference of the two limbs after exercise. When seen on December 15 she was symptom-free and there was no difference in measurement of the left and right lower limbs.

COMMENT

Supernumerary pectineal bursa is a further lesion to be considered in the differential diagnosis of swellings in the ileo-femoral region. In the case recorded the patient presented with swelling of the thigh, the cause of which remained undiagnosed until the bursa became large enough to appear in Scapa's triangle, when it was diagnosed as a femoral hernia.

Perrigard (1947) recorded this condition under the title of supernumerary bursa of pectineus muscle simulating hernia in the inguinal region. In his patient the bursa was adherent to some of the smaller tributaries of the long saphenous vein, whereas in our patient the bursa was firmly adherent to the femoral vein. In Perrigard's patient there were no symptoms referable to venous obstruction, and the bursa seemed to have been more superficial in its situation. We can find no other reference to this condition in the literature.

A similar condition which may lead to some confusion is the ileo-psoas or ileo-pectineus bursa which lies lateral to the femoral artery and may overlap the arteries and veins to lie anterior to them.

We should like to express our thanks to Dr. K. P. Ball and to Dr. Isobel Finlayson for the detail given in her original letter.

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Reviews

CLINICAL ENDOCRINOLOGY

Clinical Endocrinology. Volumes 1 and 2. By Lewis M. Hurxthal, M.D., F.A.C.P., and Natalija Musulin, B.S., M.D. (Pp. 1,599; 482 figures, 146 charts, 1 coloured plate. £9 9s. the set of two volumes.) Philadelphia and London: J. B. Lippincott Company. 1953.

This is a remarkable compilation. It comprises two large volumes totalling some 1,600 pages, all of which are packed full of facts, charts, tables, and illustrations covering the whole wide field of modern endocrinology. It is a difficult work to classify. It is certainly not a textbook; it is not an illustrated dictionary, and it is not an encyclopaedia. It is primarily a work of reference, but one of unusual and indeed impressive type. All who feel that the traditional form of textbook of medicine leaves much to be desired should give this book serious and careful consideration, for it seeks to establish a new form in a most ambitious and comprehensive manner.

The whole work consists of the systematic tabulation and classification of the known facts of endocrinology. After a short chapter on normal growth and development, which contains 19 charts, diagrams, and photographs, there follow six long chapters which together cover 1,000 pages and which deal with the functions and disorders of the traditional endocrine glands. Each of these chapters consists of a preclinical or physiological part and a more extensive clinical section. Throughout, the emphasis is on the systematic classification and tabulation of facts. The text consists almost exclusively of lists under headings and subheadings. The multiple facts seem to have been chosen and sorted with a mature judgment and are supported by a wealth of excellent illustrations, diagrams, and up-to-date references. Indeed, the clarity and profusion of the illustrations and charts are an important feature of this work. Thus the section on cretinism is followed by 39 photographs of high quality and by five charts. The section on gigantism is likewise followed by 33 equally good photographs and radiographs and by four charts. No less thorough are the series of references. For example, those relating to the anatomy and physiology of the pituitary gland number over 1,100—a classified list which alone covers 30 pages. These references appear to be well chosen and include a representative series from European and British authors. Though mainly modern, the historical references are not neglected, for Galen and even earlier authors are referred to. Later chapters in this work are more assorted. They include a comprehensive one on sterility, and others on the pineal gland, dwarfism, hirsuties, the endocrines in hypertension, gastro-intestinal hormones, antihormones, and steroids.

The advantages of a work of this type are the ease with which any particular fact may be found and the ease of access to the wide bibliography. At a test we had no difficulty in finding an answer to the question, Is the thymus enlarged in Turner's syndrome? But there are real disadvantages in a work of this type. It is not always easy to find out what to do in a given clinical situation. Thus we had difficulty in deriving a plan of investigation of the hirsute woman from the data given in the chapter on hair growth. It is also often difficult to learn from the text what is common and what is rare. A good example of this is in the list of toxic effects of antithyroid drugs used in hyperthyroidism. This list gives equal prominence to skin rashes, headaches, jaundice, and agranulocytosis among others, and does not indicate which are common and which rare. The treatment for all these complications is listed as penicillin. Ambiguities of this type can be found in other places.

A stern test of the judgment of a modern author on endocrinology is perhaps in his handling of that controversial subject, the "general adaptation syndrome." A short chapter on this concept shows commendable restraint in avoiding the many speculative developments in this field. He confines it to the more orthodox aspects of adrenal behaviour under stress, and gives a very fair survey of established facts.

This is an outstanding work conceived in the grand manner. All who have an active interest in endocrinology will find it worthy of a place of easy reference on their own shelves. It should prove particularly valuable also as a reference guide to endocrine literature in all medical libraries.

C. L. COPE.

INTRODUCTION TO PATHOLOGY

Basic Pathology and Morbid Histology. By D. B. Cater, M.A., M.D., F.R.C.S. (Pp. 330; 266 illustrations, including 20 coloured plates. 42s.) Bristol: John Wright and Sons Ltd. 1953.

The author of this book has made a valiant attempt "to help the student who has just begun the study of pathology and finds the subject difficult." He believes that the beginner in pathology, with his inadequate clinical background, comes to regard pathology as a dead science, finds that the microscopical appearances of diseased tissues are meaningless to him, and may eventually be "tempted to abandon the effort to master the subject." To rectify this sorry state of affairs, which is familiar to all those who teach pathology, the author has striven "to graft on to the student's knowledge of Physiology sufficient clinical information to make Pathology live." He tells us that the book, which is based on a one-year course of instruction, "was written for students and not for professors."

Dr. Cater's book is bursting with information, and he may be wrong in expecting the average student to acquire so much detailed knowledge in a year's preclinical course. It is possible that he would be less distressed about his students abandoning pathology if he investigated their attitude to it after three years of bedside experience, during which time they would have built up their knowledge of human pathology on the foundations provided by a preclinical course of general pathology, the success of which is usually considered to rest on the teacher's facility for skilful omission.

There are some omissions in Dr. Cater's book, and a harsh critic might consider it to be unbalanced. The word "tetanus" does not appear in the index and could not be found in the text. Syphilis is allotted a chapter of fourteen and a half pages; diphtheria is dismissed in half a page. Repair surely deserves more consideration than a detailed account of teratomata, hamartomata, and mixed tumours, and even the elementary student would like the account of fracture healing to be longer than nine lines. Regeneration is discussed in eight and a half lines. Hyperplasia does not appear in the index, and a long search in the text produced no more than a definition occupying one and a half lines. On the other hand, the pathology of tumours is most liberally treated and described with a wealth of detail and illustration, as are hypertension, renal disease, heart failure, and the anaemias and leukaemias.

In the early chapters of the book Dr. Cater makes the fullest possible use of analogy in order to fix his facts in the reader's memory, but when the story of leucocyte *versus* bacteria is compared with a full-scale battle, complete with demobilization centres, prisoners, engineers, front-line defence works, and commandos, this superficial analogy becomes rather overstrained. The author changes his literary style about a third of the way through the book, and his writing thereafter becomes quite conventional and less dramatic. One feature of this book deserves the highest commendation; the book contains a series of coloured histological drawings which are not only clear and instructive but have considerable artistic merit.

The perfect introduction to pathology has yet to be written. It may be that Dr. Cater's book will, by popularizing pathology, help in its understanding by undergraduates of average intelligence. They, after all, constitute the final court of appeal, for they alone are able to decide if they have been materially assisted by reading it.

GEOFFREY HADFIELD.

CHROMATOGRAPHY

Practical Chromatography. By R. C. Brimley and F. C. Barrett. Foreword by E. C. Bate-Smith. (Pp. 128; 34 figures. 15s.) London: Chapman and Hall. 1953.

The authors of this book describe in simple terms the various types of chromatography—adsorption, partition, and ion-exchange—and the various ways in which such chromatograms may be used—namely, elution, displacement, and frontal analysis. They then discuss working details at length, with brief references to some of the more common applications of the methods. The book ends with a chapter giving descriptions of the accessory apparatus required, such as fraction collectors and desalting apparatus.

The book fills a gap in the literature and will be found useful for those many medical research workers whose interest lies only in a particular limited application of chromatography. The literature on such a subject usually takes for granted a basic knowledge of chromatography, and without this the unfortunate potential chromatographer is forced to wade through a multitude of earlier papers gleaning little tit-bits here and there as he goes along. It is fortunate that two experienced workers have been persuaded to put aside their filter paper and columns and give us the benefit of their wide knowledge and experience.

C. E. DENT.

FATIGUE

Symposium on Fatigue. Edited by W. F. Floyd and A. T. Welford. The Ergonomics Research Society. (Pp. 196; 47 figures. £1 4s.) London: H. K. Lewis. 1953.

Some of us seem to be less worried by fatigue now that we can eat a steak at home without thinking of the protein starvation awaiting us for the rest of the rationing week. But no doubt this mixed psychological and physiological stimulus will soon pass, and we shall then have to think up other excuses for ourselves. This symposium provides a mass of solid facts on this problem, but some of the contributions are such difficult reading that they are apt to produce the very phenomenon under discussion. This is because they are highly specialized and technical contributions to already specialized aspects of a somewhat confused general problem. It is clear that some of the simplest findings remain unexplained. Psychological aspects tend to be blamed for discrepancies in physiological findings, but physiological changes may ultimately be found responsible for many of the psychological phenomena observed. As the introduction points out, the trouble lies in our present lack of knowledge of how the nervous system really works.

This book will be useful to industry, and the meeting reported was organized by a society interested in bringing together medical research workers and designers of modern machines and equipment. But little basic progress can be expected until psychological factors can be better understood in terms of altered function in the nervous system. Then there will be less need for a dualism of approach which destroys any chance of getting to the roots of the problem.

One contributor stressed the proved physiological value of limbering up before real work is begun. This symposium has the air of being this type of preliminary exercise despite the immense amount of work reported in it. Now we need another Pavlov to stimulate some sort of experimental synthesis.

WILLIAM SARGANT.

ANTIBODY RESPONSE

The Nature and Significance of the Antibody Response. Edited by A. M. Pappenheimer, jun. Symposium held at New York Academy of Medicine, March 21–22, 1951. (Pp. 227. 32s. 6d.) Columbia: University Press. London: Geoffrey Cumberlege. 1953.

This book contains fourteen articles which were presented at a symposium held at the New York Academy of Medicine in March, 1951. The science has advanced rapidly, so that there is a big gap between 1951 and 1953; but some of the authors have brought their articles up to date—Kabat, for example, quotes papers published in 1952. Chapters 1–5 are on production of antibodies, Chapters 6–9 on kinds of antibodies, and the final chapters on antigen–antibody reaction in tissues. Each article is by an authority on the subject and together they give a most valuable picture of the present state of knowledge and the problems that remain unsolved. Some of the views expressed may be criticized, but the authors have as good a right as anyone to their opinions. As Pappenheimer writes in the preface, "One positive contribution I feel confident the symposium does make: that is to demonstrate how fruitful the application of *quantitative* immunochemical methods can be in throwing light on the mechanisms of immunological reactions."

J. R. MARRACK.

TREATMENT OF SPINAL INJURIES

Injuries of the Spinal Cord. Edited by George C. Prather, M.D., F.A.C.S., and Frank H. Mayfield, M.D. (Pp. 396; illustrated. 63s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1953.

This book, with seven sections written by different authors, is essentially a manual of treatment of patients with spinal injuries and is based largely on experience of military casualties. In the neurosurgical section little is said about the physiology or the evolution of the clinical condition after complete transections of the cord. This omission is disappointing, for studies of these patients now that infection is better controlled might have added important information to knowledge of the physiology of the divided cord. The two most interesting sections are those on the urological aspects and on the nutritional problems. In the former there is an excellent account of the physiology of the "spinal" bladder and a critical account of the various methods of treatment, the author preferring a tied-in catheter or suprapubic cystostomy, either being connected to a closed drainage system with provision for manual or automatic irrigation. The importance of adequate nutrition, particularly of protein intake, has been increasingly recognized in recent years, and the chapter on nutritional aspects contains valuable information. Writers of other sections discuss in detail the plastic repair of decubitus ulcers and methods of rehabilitation and the treatment of associated injuries, and there is an interesting if somewhat discursive account of the psychology of the paraplegic. This book is a useful manual of treatment.

J. W. ALDREN TURNER.

ELECTRICAL HEART PICTURE

Das Elektrische Herzbild. By Dr. Wilhelm Ernsthausen. (Pp. 231; 227 figures. M.48.) Munich: Verlag für Biophysik, Hermann Rinn. 1953.

"The electrical picture of the heart," to translate the title of this work literally, will in all probability be outside the range of the average clinician. A mathematical equipment beyond the ordinary is needed to follow the arguments. Here and there, however, the reviewer has managed to glean some interesting information. The second chapter on the chemical elements concerned in the contraction of the muscle cells is interesting and illuminating, for there are some good illustrations which give a clear conception of the chemical structure of a muscle cell. The author puts forward the theory that relaxation is really an active process. In the next chapter he describes the movement of ions and the formation of energy. The control of metabolism is discussed from the aerobic and anaerobic aspects. From now on the subject-matter becomes very difficult, not only in itself but in the German. No doubt someone interested in advanced physiology will find it intelligible, but the complexity and multiplication of the hundred or so cardiograms which go to make up the "electrical heart picture" may well prove too obscure for the ordinary cardiologist for a long time to come.

TERENCE EAST.

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THE MEDICAL TREATMENT OF PEPTIC ULCER

No matter how well the cause of a disease may be understood, nor how self-evident the rational treatment may appear to be, the proof of the efficacy of that treatment remains the observation that in practice it works. When, on the contrary, as is the case with peptic ulcer, knowledge of causation is rudimentary, it is all the more essential that treatment should be firmly based on the results of scientific trial. Yet the current medical treatment of peptic ulcer is more dependent on tradition, clinical impression, and armchair speculation than any other branch of therapeutics.

The reason is not difficult to understand. It lies essentially in the natural history of the disease, which is one of a continual succession of relapses and remissions, spread over a lifetime and punctuated on only rare occasions, if at all, by the complications of haemorrhage, perforation, or obstruction. Hence any form of treatment may readily be shown to be followed by improvement in a large proportion of cases. And if it can be shown that the treatment may in certain circumstances neutralize or reduce the secretion of gastric juice, a theoretical explanation for its efficacy has been obtained which may serve to establish it firmly in the body of customary teaching. Physical rest, the avoidance of mental conflict, the ingestion of frequent and bland meals, alkalis, antispasmodics, secretory depressants, and sedatives are all regularly advised as essential parts of a regime which must be adhered to, more or less strictly, if the symptoms are to be kept under control—and this, as Todd[1] has pointed out, despite the recognition that polypharmacy is nearly always a cloak for ignorance.

With increasing appreciation of the natural history of ulcer and of the ease with which therapy may obtain the credit properly due to time alone, it has become accepted in this country that a fresh treatment must run the gauntlet of a planned clinical trial before it can reasonably be adopted for routine use. Consequently, although more than a score of new treatments (some entirely new,[2 3] some variants of older methods[4 5]) have been put forward since the war, none has gained general acceptance. Moreover, the justification for standard therapy is now increasingly often being questioned.

Elsewhere in this issue Dr. P. R. C. Evans reports the results of a trial of the proprietary product "robaden" and of the value of a strict dietetic regime accompanied by a number of conventional drugs. Robaden is a Swiss preparation extracted from the stomach and small intestine of animals; it is free from lipoids and proteins, and is therefore distinct from enterogastrone. It has been claimed that robaden can bring about the healing of ulcers produced by histamine injection in guinea-pigs even when the injections are continued, and numerous enthusiastic reports of its value in man have appeared in the Continental literature (the makers advise the use of robaden for out-patients in conjunction with a normal diet). The conclusions derived from controlled trials have, however, been distinctly different. Bubb[6] obtained better results with bed rest and standard diet, and Stolte,[7] in a model investigation, obtained equally beneficial results from an inert placebo. Evans's results are in complete conformity; out of a total of 45 patients given robaden he assessed 24 as failures (53%), while of 53 patients given similar injections and tablets known to be inert 25 were failures (47%).

Evans's more important, and possibly more surprising, observation was that 51% of patients (that is, 27 out of 53) had eventually to be classified as failures after a course of four weeks' hospital treatment on a strict gastric diet, with bed rest and administration of phenobarbitone, hyoscyamine, olive oil, and magnesium trisilicate. In comparison there were 49% of failures (22 out of 45) among those who were given four weeks' in-patient treatment on a simple convalescent regime, allowed up two hours daily, and given no drugs other than magnesium trisilicate when necessary to relieve pain. The comparison is perhaps not quite fair to the stricter treatment, since "failures" included patients who relapsed at any time during the follow-up period of (on the average) two to three years, and for the greater part of the follow-up both groups of patients were given similar treatment regimes. Comparison of the results immediately after the end of the in-patient treatment might have shown a different picture, but so far as

[1] *Lancet*, 1952, **1**, 113.
[2] Cheney, G., *J. Amer. diet. Ass.*, 1950, **26**, 668.
[3] Page, R. C., and Heffner, R. R., *Gastroenterology*, 1948, **11**, 842.
[4] Co Tui, Wright, A. M., Mulholland, J. H., Galvin, T., Bareham, I., and Gerst, G. R., ibid., 1945, **5**, 5.
[5] Kemp, S., *Nord. Med.*, 1948, **40**, 1979.
[6] *Schweiz. med. Wschr.*, 1949, **79**, 663.
[7] *Lancet*, 1950, **2**, 858.
[8] *Quart. J. Med.*, 1953, **22**, 439.
[9] *Lancet*, 1952, **1**, 482.
[10] Ibid., 1954, **1**, 386.
[11] Ibid., 1952, **1**, 171.

the practical implications are concerned this is of little importance, since within a short interval any presumed advantage was already lost.

Surprising though this result may seem, it is not out of line with other recent work. Rae and Allison,[8] for example, studied 63 patients with ulcers who were all in the Royal Navy and who were provided with the most suitable environmental and dietetic conditions for a period of a year as part of an experimental scheme for the rehabilitation and employment of men with peptic ulcers. They reinvestigated the group five years later, when all but one had returned to civilian life, and concluded that "in this series of patients the natural history of the disease was not materially influenced by the prolonged medical treatment." In a series of 140 patients Lawrence[9] found no advantage in strict dieting compared with the use of ordinary hospital food. Among 125 patients with duodenal ulcer treated ambulantly with various drugs, including hexamethonium, methantheline, and olive oil, Friendlander[10] was unable to detect any significant beneficial results; and Doll and Pygott[11] could find none among gastric ulcer patients treated with phenobarbitone. The last-named workers did, however, observe more rapid healing among patients who were treated in bed in hospital than among those who continued at work, while Lawrence confirmed the value of alkalis for the relief of pain.

On the evidence, therefore, it would seem that the value of any form of dieting or of any drugs other than alkalis (and these only for the relief of pain) must be considered unproved. Even continuous milk-drip has not been shown to accelerate the rate of healing significantly, though it is probably of value for the alleviation of persistent pain. Nevertheless, until further evidence accumulates, the weight of clinical impressions should not altogether be disregarded any more than should the patients' oft-reiterated statement that fried foods (or cheese or apple as the case may be) aggravate their pain.

ION-EXCHANGE RESINS

In 1935 Adams and Holmes[1] published their methods for the preparation of ion-exchange resins. These consist of a highly insoluble organic matrix containing as many centres as possible at which cation or anion exchange can occur. In the cation-exchange resins used in medicine these centres are of two kinds, carboxylic (COOH) and sulphonic acid (SO_3H) groups, the latter being active over a wider range of *p*H though having a lower exchange capacity than the former.[2,3] Their affinity for cations decreases in the following order: $Ca^{++} > Mg^{++} > K^{+} > Na^{+} > NH^{+} > H^{+}$.[4] They yield hydrogen ion in exchange for the cation which they absorb; and, since this tends to cause buccopharyngeal ulceration, when they are used for clinical purposes ammonium is usually substituted for the hydrogen ion, the resin then being said to be in ammonium phase or cycle. Whichever cycle the resin is in, the metabolic effect is the same. Acidosis is produced by the absorption of hydrogen ion in the one case, or in the other results from the absorption of NH_4 and the subsequent conversion of NH_3 to urea in the liver, leaving hydrogen ion to be covered and excreted. The exchange capacity of different resins *in vitro* is conditioned by a number of different physico-chemical factors,[2] and it has been disappointing to find that *in vivo* they exert only about 25 to 40% of their *in vitro* binding power for cations.[5,6] There have been various theories to account for this.[7-9]

In the *Journal* this week at page 603 Drs. A. G. Spencer, E. J. Ross, and H. G. L. Lloyd-Thomas describe their experiments on the uptake of isotopic sodium and potassium by a cation-exchange resin *in vivo*. Their results indicate that the uptake of sodium greatly exceeds that of potassium in the small gut except in the jejunum, where the presence of dietary potassium, especially when this exceeds the sodium intake, favours the uptake of potassium. Lower down in the small intestine the absorbed potassium is displaced by sodium; but in the colon the process is reversed, and sodium is lost from the resin in exchange for potassium. This is more marked in patients on a low sodium intake, partly at least because of the enhanced efficiency of the normal reabsorptive function of the colon which occurs in sodium depletion. The authors liken the presence of a resin in the gastro-intestinal tract to that of an artificial electrolyte-containing compartment in the organism, a compartment which is constantly exchanging its ions with those of the rest of the organism in a continuing series of dynamic equilibria. This emphasis on the dynamic aspects of

[1] *J. Soc. chem. Ind.* (*Lond.*), 1935, **54**, 1T.
[2] Duncan, J. F., and Lister, B. A. J., *Quarterly Reviews*, 1948, **2**, 307.
[3] Dock, W., and Ferguson, F. C., *N.Y. St. J. Med.*, 1953, **53**, 75.
[4] Nachod, F. C., *Ion Exchange, Theory and Application*, 1949, New York.
[5] Ch'en, J. S., and Freeman, S., *J. Lab. clin. Med.*, 1950, **35**, 99.
[6] McChesney, E. W., and McAuliff, J. P., *Amer. J. Physiol.*, 1950, **160**, 264.
[7] Hegsted, D. M., *et al.*, ibid., 1951, **164**, 695.
[8] Fourman, P., *British Medical Journal*, 1953, **1**, 544.
[9] Berger, E. Y., and Steele, J. M., *J. clin. Invest.*, 1952, **31**, 451.
[10] Steinberg, A., *Proc. Soc. exp. Biol., N.Y.*, 1944, **58**, 124.
[11] Segal, H. L., *et al.*, *Gastroenterology*, 1945, **4**, 484.
[12] Spears, M. M., and Pfeiffer, M. C. J., ibid., 1947, **8**, 191.
[13] Martin, G. J., and Wilkinson, J., ibid., 1946, **6**, 315.
[14] Segal, H. L., *et al.*, *Amer. J. dig. Dis.*, 1950, **17**, 293.
[15] Neuhauser, I., and Gustus, E. L., *Arch. intern. Med.*, 1954, **93**, 53.
[16] Segal, H. L., *et al.*, *Proc. Soc. exp. Biol.* (*N.Y.*), 1950, **74**, 218.
[17] Harkness, J., and Durant, J. A., *J. clin. Path.*, 1953, **6**, 178.
[18] Bull, G. M., *Proc. roy. Soc. Med.*, 1952, **45**, 848.
[19] *Trans. Ass. Amer. Phys.*, 1946, **59**, 282.
[20] Payne, W. W., and Wilkinson, R. H., *Lancet*, 1951, **2**, 101.
[21] Lippman, R. W., *Amer. J. Med.*, 1951, **10**, 776.
[22] Mateer, F. M., *et al.*, *J. clin. Invest.*, 1951, **30**, 1018.
[23] Greenman, L., and Danowski, T. S., *Penn. med. J.*, 1952, **55**, 563.
[24] Friedman, I. S., *et al.*, *Amer. J. med. Sci.*, 1951, **221**, 672.

the mode of action of resins contrasts with the somewhat static part they have been assigned in many of the theories which have been advanced hitherto.

In the nine years immediately following their discovery the properties of ion-exchange resins were applied solely to chemical laboratory processes. A cation-exchange resin was first used in a medical laboratory to prevent blood clotting *in vitro* by exchanging sodium for the calcium of the blood.[10] Later, anion exchangers were found to neutralize the free acid of the gastric secretion and were used therapeutically in cases of peptic ulceration[11–14]; more recently complexes of anion-exchange resin and fatty acids have been used for the treatment of intestinal moniliasis.[15] Cation exchangers yielding quinine for hydrogen ion have been used to detect the presence of free acid in the gastric secretion in tubeless gastric analysis,[16 17] and to deplete body potassium in cases of hyperkalaemia due to renal failure.[18] Following a suggestion by Dock[19] that resins could divert from absorption most of the sodium ingested by patients with oedema, they have been used mostly for this purpose.

On page 597 of this issue Drs. Spencer and Lloyd-Thomas describe their experience with the use of cation-exchange resins in the treatment of 39 patients with oedema, 30 having cardiac and 9 renal disease. Seven patients had only minimal oedema, and of the 32 with gross oedema 65% showed marked improvement after resin treatment. The authors point out, however, that the resins were given as adjuvants to other measures, such as rest in bed, a low sodium diet, and fluid restriction, which in themselves are often sufficient to cause improvement and delivery of the oedema. 67% of the patients complained of discomfort, which was mainly gastrointestinal, and it was more marked in patients treated with the hydrogen-cycle resin given in the early stages of the investigation. A unique complaint of alopecia was made by one patient. 48% of patients developed clinical signs of potassium depletion, some with characteristic electrocardiographic changes and sensitization to digitalis. This was directly related to potassium intake, and occurred less often in patients who received 25% of the resin in the potassium cycle. Apart from this, biochemical distortions were common though rarely serious and included a compensated increase in plasma chloride, which rose to hyperchloraemic levels in only six patients with early renal failure, who developed clinical signs of acidosis, whereupon resin treatment was stopped.

In their renal cases Spencer and Lloyd-Thomas found that resin treatment was not contraindicated so long as there was no impairment of the kidney's capacity to form ammonia to cover the excretion of acid, but that where initially there was uraemia and renal impairment resin treatment was contraindicated. There are many reports of the favourable effects of adjuvant treatment with resins on the oedema of the nephrotic syndrome,[20–23] but most warn of its dangers in patients with a low renal reserve. The dangers are four: first, of causing an acidosis in patients whose ability to form ammonia is impaired; secondly, if an admixture of resin in potassium-cycle resin is given, of causing hyperkalaemia; thirdly, of contributing largely to the nitrogen intake with ammonium from ammonium-cycle resins; and, fourthly, of causing or aggravating structural damage in the kidney, for even healthy subjects taking resins have been shown to pass granular casts transiently in their urine.[24] Since Type II nephritis is the most common form of the nephrotic syndrome, and since it is a stage in progressive nephritis, it is questionable whether resin treatment should be used at all in this disease.

It is clear that treatment with ion-exchange resins requires careful biochemical control, and this raises the question whether they can be used safely in domiciliary practice. Spencer and Lloyd-Thomas found that they could, provided the necessary chemical estimations could be carried out every two to four weeks, and the answer really hinges on whether these can be done within a reasonable distance of a patient's home. Without such facilities, resin treatment for oedema, whether of cardiac or renal origin, would be dangerous.

WHOLE-TIME SPECIALIST APPOINTMENTS

The large majority of the medical profession has been consistently opposed to a whole-time salaried service: the plebiscite of the whole profession in 1948 left no doubt about that. Medical men and women entered the Service only on the promise—subsequently written into the Amending Act of 1950—that a salaried service would not be brought in by regulation. It is fair to say that the profession's opposition to a salaried service has been non-political, in so far as that is possible in an issue forced into the political arena, and came from a conviction that such a service would be bad for the public and the profession. The Royal College of Physicians in its evidence to the Guillebaud Committee, which we publish in this week's *Supplement* (p. 69), sums up the pros and cons of whole-time service and clearly presents what is the viewpoint of most doctors. It is the measured answer to Opposition questioners who in the house last week sought to persuade the Minister of Health—and, no

doubt, Mr. Guillebaud too—that a whole-time hospital specialist service would be more efficient and economical (see "Medical Notes in Parliament," p. 653).

Discussing the advertising of whole-time vacancies, the *Lancet* recently remarked on the preference of some boards for whole-time appointments and the preference of most consultants for part-time appointments, and went on to say that, "until a coherent policy has been adopted, there seems to be no reason why a board should not be able to advertise a full-time post if it has 11 sessions which it wishes to be undertaken by one consultant."[1] But, while opinions may differ about individual appointments, the policy on matters of principle has been settled. In 1948 the Ministry sent a circular to hospital authorities in which it was said that in assessing their staffing needs authorities should take into account so far as possible the individual consultant's wishes about his terms of service and that whole-time appointments should be made only where the requirements of the Service made such appointments necessary. This directive, as the Minister made clear in the House last week, has remained the policy of the Ministry ever since. However, in 1952 the Representative Body of the British Medical Association, meeting at Dublin, resolved that advertisements for new whole-time consultant or S.H.M.O. posts should not be accepted for publication in the *Journal* except with the approval of the regional consultants and specialists committee. This resolution rose out of a belief that some regional boards were wilfully misinterpreting the terms of the 1948 circular and were advertising more whole-time vacancies than were strictly necessary for the needs of the Service. It was later agreed between the Joint Consultants Committee and the Ministry that where there was objection by the local consultants to the advertisement of a new whole-time post it should be referred to the Ministry through the Joint Committee for discussion before the Association finally rejected the advertisement.

That is how the matter stands at the moment. Obviously the needs of the Service vary somewhat in different regions, and the boards must have some discretion in the administration of their area. At the same time they should realize that the staffing needs of their hospitals are best known by the hospital specialist staffs themselves. The profession has long sought to establish that hospital administrative bodies at all levels should seek the advice of representative professional committees on specified matters. This position has now been achieved with hospital management committees and boards of governors but not with regional boards. Regional consultant committees would be suitable bodies to advise boards on such matters as staffing requirements, but, as they are not called into consultation, the present policy of refusing advertisements of whole-time posts at their request is the only way of making their voice heard effectively on a matter of importance. If it checks certain boards in their trend towards creating a whole-time specialist service, it is a check which the majority of the profession would support.

[1] *Lancet*, March 6, 1954, p. 527.

IMMUNIZATION AGAINST POLIOMYELITIS

Recent reports in the daily press that the Queen and the Duke of Edinburgh have been given injections intended to protect them against poliomyelitis in an epidemic area of Australia may have caused a widespread impression that there is now some effective method of active immunization against this disease. We are given to understand that the material used was gamma globulin, which is calculated to afford passive protection for the limited period of the royal visit to the area in question. In these very special circumstances no one will question the wisdom of taking this quite harmless precaution, even though absolute proof of its efficacy does not exist. In a disease with so low an attack rate as poliomyelitis, and one of which the dissemination is so mysterious that we cannot know whether or when any given individual has been exposed to infection, it is not surprising that extensive use of gamma globulin in the United States has failed to afford this proof. On the other hand experimental, as distinct from clinical, test is reassuring. Bodian[1] found that gamma globulin possessed a high degree of neutralizing power against all three types of virus, as judged by infectivity for monkeys, even though the blood from which it was derived was collected mainly in a part of the United States in which the Leon type of virus has never been isolated.

Active immunization presents the most formidable difficulties, greater perhaps than those for any other infectious disease. There are three immunologically distinct types of virus; they can be propagated only in tissue culture and thus on a very small scale. The use of animal cord suspensions, the only ready source of virus, is not altogether without risk of causing secondary changes in the central nervous system. Moreover, according to McHammon[2 3] even in an epidemic area it would be necessary to inoculate 11,000 children to prevent one fatal or paralytic case, and in a non-epidemic perhaps 50,000. Many will remember the disaster of twenty years ago when two vaccines were

[1] *Proc. Soc. exp. Biol. (N.Y.)*, 1949, **72**, 259.
[2] *Pediatrics*, 1950, **6**, 696.
[3] Ibid., 1951, **8**, 741.
[4] *J. Amer. med. Ass.*, 1935, **105**, 2152.
[5] Ibid., 1953, **151**, 1081.
[6] *Amer. J. Hyg.*, 1952, **55**, 108.
[7] *Proc. Soc. exp. Biol. (N.Y.)*, 1953, **82**, 277.
[8] *J. Immunol.*, 1951, **67**, 213.
[9] Ibid., 1951, **67**, 219.

introduced in the United States in which the virus was supposed to be attenuated by chemical means, in the Kolmer vaccine with 1% sodium ricinoleate and in the other with 0.1% formalin. A report by the medical director of the United States Public Health Service[4] describing twelve cases of poliomyelitis apparently resulting directly from injection of one of these vaccines, five being fatal, led to the abandonment of both.

A vaccine now undergoing clinical trial is that prepared by Salk and his colleagues.[5] It is derived from roller-tube tissue cultures of monkey testicle or kidney, and includes all three types of virus, inactivated by treatment with 0.4% formalin. This has been found to induce antibody formation of similar degree to that resulting from natural infection. A perhaps more promising development, although only in an early stage, is the work of Koprowski and his colleagues[6 7] on the use of an oral vaccine. It has been known for some years that antibody formation may result from the oral administration of certain strains of living virus in monkeys. Melnick and Ladinko,[8 9] using the Y-SK variant of Lansing virus, obtained this consistently, although a few animals also developed paralysis. Koprowski and his colleagues have used the TN strain, which, having been adapted to the cotton rat, lost pathogenicity for monkeys. Successful trials in chimpanzees were followed by the administration of a suspension of infected cotton-rat brain and cord orally, first to one non-immune human volunteer and then to nineteen others, of whom fourteen were non-immune. No symptomatic effects of any kind resulted. Of the fifteen non-immunes, twelve had virus in their faeces more than four days after vaccination—that is, at a stage when passive elimination would not account for its presence—and neutralizing antibodies in high concentration appeared in the serum of these subjects and of three others in whose faeces virus was not detected. This trial was then extended to sixty-one non-immune mental defectives with similar results, in which the additional observation was made that virus does not appear in the blood. This method has obvious advantages, as well as the merit of imitating the process by which immunity is naturally acquired.

GREAT ORMOND STREET AND KAMPALA

It is now perfectly feasible for a patient to have afternoon tea in tropical Africa and have breakfast next morning in a London hospital. It follows from this that hospital staffs in this country will be the better equipped to answer any calls that may be made on their services if they possess, through personal experience, a knowledge of tropical conditions and the approach to tropical diseases which is at present largely confined to those who have served in our Colonial Medical Service. This is one of the several important reasons why active co-operation between hospitals in this country and those in the Tropics should be encouraged. Last week plans were announced of an admirable scheme for fostering close relations between the Hospital for Sick Children, Great Ormond Street, and the medical faculty of Makerere College, Kampala, Uganda. Each year a member of the visiting staff of Great Ormond Street will spend some weeks in Uganda; a senior medical registrar will spend approximately two years in Kampala; and one or two nursing sisters will be seconded to staff the children's ward at Mulago Hospital, Kampala. This hospital is the teaching hospital for the medical school of Makerere College, and is reserved entirely for African patients. It forms part of the Uganda Medical Service, while Makerere College and its medical school are maintained by the three territories of Uganda, Kenya, and Tanganyika. This offers a close analogy to the teaching hospitals at home, which are now the property of the Minister of Health, while the medical schools conform to university standards: the same smooth relationship which exists between the teaching hospitals and the medical schools in Great Britain also animates the hospital and medical school at Kampala.

The study of what may widely be termed tropical paediatrics is still a young subject, to which the work on kwashiorkor carried out at Mulago has given a noteworthy stimulus. While there is no dearth of clinical material nor of paediatric problems in Uganda itself, Mulago Hospital, situated only eighteen miles from the airfield at Entebbe—an important junction on the London–South Africa air route—may well develop an increasing importance for large tracts of the African continent. When, a few years ago, the visitors of the General Medical Council made their report on Makerere medical school, they commented upon the lack of adequate facilities for paediatric education. Last summer, at the time of the Coronation, a meeting was held at the Hospital for Sick Children, Great Ormond Street, between representatives of that hospital and the Uganda Medical Service and Makerere College medical faculty, at which the birth of an association between the hospital in London and the paediatric services at Mulago was planned. Later two members of the Great Ormond Street staff visited Kampala, and were able to give a favourable report on the gestational progress. The liaison is now complete, for already a sister has left London for Mulago to take charge of the children's ward, and in the autumn the first of a flow of senior registrars is to be seconded for a period of two years to take part in the work and teaching of the paediatric department. This association between a London teaching hospital, the East African university, and the Uganda Medical Service will be warmly welcomed.

The Council of the B.M.A. at its meeting on March 9 unanimously decided to award the Gold Medal of the Association to Dr. S. Wand in recognition of his outstanding services to the Association and to the profession. Dr. Wand is chairman of the Representative Body. A member of the Insurance Acts Committee from 1937 to 1948 and of its successor, the General Medical Services Committee, since 1948, he was chairman of the committee during 1948–52. During these years he gave untiring and distinguished service in the negotiations on behalf of general practitioners which culminated in the Danckwerts award.

CLINICAL PATHOLOGY IN GENERAL PRACTICE

TESTS FOR VENEREAL DISEASE—II

BY

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The method of taking serum from a suspected syphilitic primary sore has been described in Part I (March 6, p. 575), and the finding of *Treponema pallidum* by dark-ground examination is proof of the disease. One negative finding is not conclusive evidence that the patient is not harbouring the parasite, and it may be that three or four attempts at daily intervals may be necessary for success. During this time the lesion should be protected and bathed with normal saline as opportunity serves. Should any difficulty arise it might be wise to send the patient to the pathologist.

Blood Tests for Syphilis

Blood tests for syphilis include the standard serum tests and Nelson's treponemal immobilization test. The former tests are usually reported as being negative or positive, with neat serum or dilutions thereof. The strength of a reaction (the higher the serum dilution the stronger the reaction) is no indication of the "amount" of the infection, but rather a reflection of the reaction of body tissues to the disease. Time should never be wasted in taking specimens of blood from the umbilical cord of infants. Such specimens when they arrive at the laboratory are nearly always infected, thus vitiating precipitation tests, or are anti-complementary to such a degree that they cannot be tested by a complement-fixation test.

Standard serum tests for syphilis and their modifications are legion, but all come under two headings: (1) complement fixation—for example, Wassermann tests, using standard or cardiolipin antigens; and (2) precipitation tests (including the clarification tests) such as the Kahn, Meinicke, Venereal Diseases Research Laboratory (Chambleé, U.S.A.), and Price's precipitation reaction.

Most laboratories employ a Wassermann reaction as the standard test, and a precipitation test as a check. It is important to seek the advice of the serologist concerning the relative sensitivity of the tests on which the report is based before attempting to assess the results. Fig. 1, in

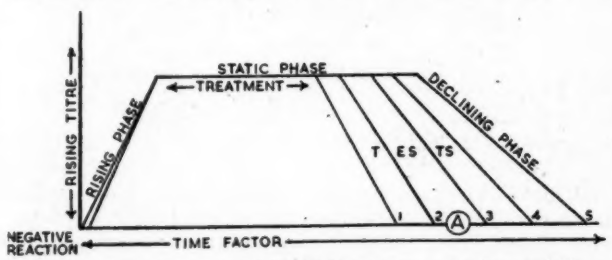


FIG. 1.—Relative sensitivities of five serum tests for syphilis.

which five serum tests for syphilis are depicted, illustrates this point. There is little difference during the rising phase in the sensitivity of any of these tests. Thus in the early stages of the disease one is not likely to become positive much earlier than the others. In the static and declining phases marked differences are evident. Thus test 1 stays static for the shortest time and becomes negative before any of the others. It is followed by tests 2, 3, 4, and 5. If, therefore, a blood were tested by these five reactions at time point A, the report would read: tests 1 and 2 negative, tests 3, 4, and 5 positive. Lack of knowledge of the relative sensitivities of the various tests would make the interpretation of such a report difficult.

It must be made clear that *in the absence of any clinical signs* a diagnosis of syphilis should *never* be made on the strength of positive tests obtained with one blood specimen. When such an occasion arises, it is unwise to inform the patient that he or she is suffering from syphilis. The history and clinical condition should be reinvestigated, and the possibility of a non-treponemal reaction (so-called biological false positive) discussed with the pathologist before any action is taken.

Non-treponemal Reactors

In Britain non-treponemal reactions (approximately 0.3% of all bloods tested) are most commonly obtained with bloods from patients suffering from atypical pneumonia and bronchial infections, from antenatal patients, and from those who have been vaccinated recently for smallpox or inoculated with T.A.B.C. vaccine. It follows therefore that when standard serum tests are being performed for emigration purposes the blood specimen should be taken before vaccination or inoculation is performed. Rarer causes of non-treponemal reactions are haemolytic anaemia and some cases of lupus erythematosus. In my experience glandular fever was possibly responsible for only one non-treponemal reaction when sera from 92 patients suffering from this disease were tested. In the conditions listed above the serum may, on serial testing and in the absence of any antisyphilitic treatment, remain positive at a low titre for a relatively short time (three months) before gradually fading in strength until it becomes negative.

The real difficulty arises in the case of antenatal patients, for time is short. Here Nelson's treponemal immobilization test may be of value, but the pathologist should be consulted before asking for this investigation. The test is so complex and time-consuming that it cannot be regarded as a routine test; it must be reserved for special "problem" sera. At least 10 ml. of blood taken with aseptic precautions into a sterile container is required, and the results are reported in percentage terms of immobilization. Thus 100 to 50% immobilization is a positive reaction, 50 to 20% a doubtful reaction, and 20 to 0% a negative reaction. Because the living *Treponema pallidum* is used as an antigen the test is said to be specific, and so far few non-treponemal reactions have been substantiated. One other serum test can be used with the blood of suspected non-treponemal reactors—the Kahn universal serological reaction. The serum is tested by a series of quantitative reactions using different solutions of saline. The results are read immediately as well as after 4 and 18 hours at 4° C. Different serological patterns are thus obtained, one of which is said to be typical of a syphilitic serum.

Chronic non-treponemal reactions are more difficult to deal with because serial blood testing may consistently yield positive results for years before the test returns to negative, and this in the absence of any family or clinical history, signs, or treatment of the disease. In fact it may be almost impossible to decide whether a patient is suffering from latent syphilis or whether he is a non-treponemal reactor. In such cases the treponemal immobilization test and Kahn's universal reaction may be of help. The decision to treat or not to treat can be extremely difficult, and if confronted with such a dilemma the practitioner is strongly advised to consult a venereologist.

Serological Patterns in Syphilis

Interpretation of serum-test reports depends, therefore, on the knowledge of the methods of reporting and the sensitivity of tests as well as on the behaviour of the tests during the course of the disease. Fig. 2 depicts a typical sero-

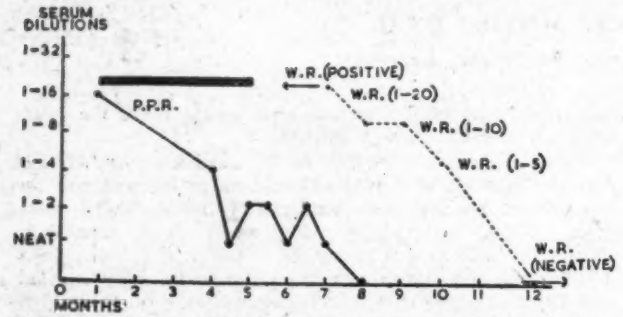


FIG. 2.—Typical serological pattern in a case of untreated latent syphilis of four years' standing, discovered on routine testing at beginning of treatment for gonorrhoea. The black rectangle indicates period of antisyphilitic treatment. P.P.R. = Price's precipitation reaction. W.R. = Wassermann reaction.

logical pattern of a patient with a positive serology tested throughout by means of the standard Wassermann reaction and Price's precipitation reaction. It will be noted that the latter returns to negative four months earlier than the Wassermann reaction in the absence of any further treatment.

Another but more complicated serological pattern of a patient is depicted in Fig. 3. Here, in spite of treatment, two sero-relapses occurred during the course of the disease before the blood tests returned to negative.

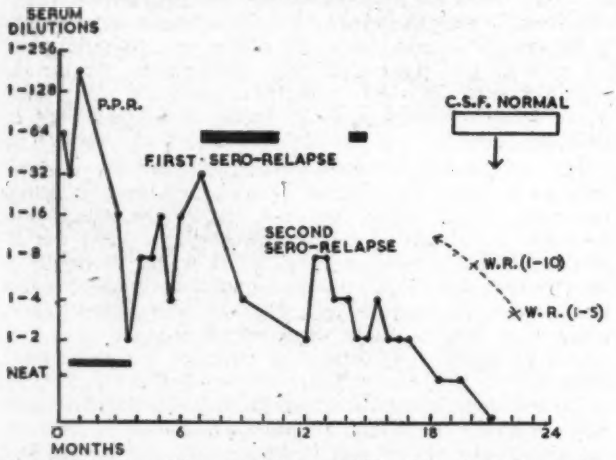


FIG. 3.—A case of late secondary syphilis with a healed pustular rash. Two sero-relapses occurred in spite of treatment.

"Oscillatory" phenomena, mentioned in connexion with the gonococcal complement fixation test, occur also with the standard serum tests for syphilis, and Fig. 4 depicts this phase of syphilitic serology. These types of reactions usually mean that the positive result is well on its way to becoming negative.

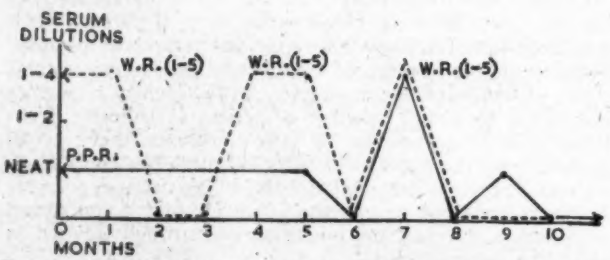


FIG. 4.—"Oscillatory" phase in the serology in a case of early latent syphilis of less than one year's standing.

A serological relapse may be said to have occurred when a series of three consecutive rises in titre are obtained by routine tests at short intervals during the course of management of syphilis. An example of this is shown in Fig. 2. Such a pattern may precede a clinical relapse.

"Carry-over" reagin is the term given to reagin which has passed from a sero-positive mother's blood to that of her newborn infant. Usually the serum titre of the mother is higher than that of the child, but the latter's positive serum reaction rapidly returns to negative in the course of six to eight weeks. Therefore if a child born of a syphilitic mother has no signs of the disease it should not be treated merely on the strength of a positive blood reaction. Quantitative serial blood testing at fortnightly intervals will soon reveal the course of events.

In general, once a diagnosis of syphilis has been made it is necessary to perform routine blood tests at suitable intervals in order to obtain a clear appreciation of the serological pattern, which indicates the response to treatment. The timing of blood tests must be left to the clinician, but it is suggested that the blood should be tested at monthly intervals for three months after treatment; thereafter, provided the clinical condition is satisfactory and the serum tests are negative or the titres are on the down grade, at three-monthly intervals for a year, followed by six-monthly intervals for another year. If all has gone well, a final blood test one year later should be performed. Variations in this scheme must depend on the response of the patient both clinically and serologically.

Cerebrospinal Fluid in Syphilis

All cases treated for syphilis should have their cerebrospinal fluid examined at least twice before being discharged as cured. In primary and secondary syphilis the usual times are at the end of the first six months of treatment and just before final discharge. Patients who come for diagnosis at a later stage of the disease should have their cerebrospinal fluid tested before treatment is given. Tests thereafter are taken at times which will depend on the diagnosis and the clinician's assessment of the effect of treatment.

Earle Moore's Classification of Spinal Fluid Patterns in Syphilis

Group	Cell Count	Protein Content (mg./100 ml.)	Wassermann Reaction	Lange Test
Normal	9 or less, usually 5 or less	40 or less	Negative	0000000000 to 2111000000 or 0112100000
1	10 or more, usually less than 50	40 or more, usually less than 100	"	As in normal fluid, or, e.g., 3210000000
2	10 or more, usually less than 200	40 or more, usually less than 100	Positive	Variable readings
3	10 or more, usually (except in acute syphilitic meningitis) less than 500	40–200 or more	"	First zone or "paretic" curve. 4321000000 to 5555554321

If the Wassermann reaction is negative, the total protein estimation below 30 mg. per 100 ml., the cell count less than 10 per c.mm., and the Lange colloidal gold test normal, the result can be regarded as satisfactory. Any deviation from these standards may merit a close re-examination of the patient's mental and physical condition. It has been stated, however, that minimal amounts of reagin can leak through from the blood stream into the cerebrospinal fluid (possibly through the choroid plexus) with the result that a patient with a positive blood test may have a weakly positive cerebrospinal fluid (Wassermann reaction positive with neat fluid) in the absence of any clinical signs or increase in the total protein and number of cells. The interpretation of cerebrospinal fluid reports can be extremely difficult, and Earl Moore's* classification will be found to be helpful (see Table).

J. vener. Dis. Inform., 1949, Suppl. 23, p. 66.

Group 3 is a "paretic formula" and is usually obtained with the cerebrospinal fluid of all untreated cases of paralytic dementia. This pattern can occur with other clinical forms of neurosyphilis, or even with asymptomatic neurosyphilis. When this happens the report should carry a warning to the clinician that unless the patient is treated adequately there is a grave risk that he may develop paresis. It should be realized that the cerebrospinal fluid can be normal in untreated neurosyphilis, especially in tabes dorsalis (20%) or in vascular neurosyphilis. In interpreting the results of the examination of cerebrospinal fluids, it is a good working rule to remember that the degree (or absence) of active inflammation in the nervous system (usually the meninges) is measurable by the cell count and protein content. If either or both remain high after treatment for neurosyphilis the patient should be treated again. On the other hand, if the cells and protein content recede to and remain normal, this is evidence of improvement of the inflammatory condition even if the Wassermann reaction and Lange test remain static. However, the findings in the cerebrospinal fluid of some cases of neurosyphilis (especially tabes) can show improvement in both cell count and protein, even in the absence of any treatment.

In cerebrospinal syphilis, therefore, the pathological report must be appraised with the following facts in mind: (1) the Wassermann reaction is used to exclude or confirm syphilis as the cause of an inflammatory condition; (2) the cell count and protein estimation are used as measures of the inflammation; and (3) the Lange colloidal gold reaction detects changes in the globulin/albumin ratio of the cerebrospinal fluid which occur not only in neurosyphilis but also in other infections of the central nervous system. In neurosyphilis three well-defined types of reactions are usually described—namely, the paretic curve 5555432100, the tabetic 0014321000, and the meningeal 0001234320.

Lymphogranuloma Inguinale (Lymphogranuloma venereum)

Lymphogranuloma inguinale is a disease due to a virus, in the diagnosis of which the laboratory can render considerable help. Of the two tests employed, the Frei skin test is the more important. The antigen (0.1 ml.) is injected intradermally in the forearm so that a weal is raised. In positive reactions an inflammatory infiltration or nodule measuring 6 mm. in diameter with a surrounding zone of erythema is present within 48–72 hours. The antigen used is a standardized culture of infected yolk of chick embryo, whilst the control test is made with material from uninfected yolks. The other test is a complement-fixation reaction, and a titre of 1 in 16 or more obtained with the serum of patients who have a positive Frei reaction is strong evidence of infection. Standard serum tests should always be performed to exclude a coexisting syphilitic infection.

Granuloma Inguinale

Granuloma inguinale is a rare disease in this country, and the diagnosis is permissible only when Donovan bodies are found in the smears or when pathognomonic cells are demonstrated by biopsy. If the practitioner suspects that a patient may be suffering from this condition it is suggested that a venereologist should be consulted.

Addenda

Before leaving the subject of tests in venereal diseases one other investigation should be mentioned—namely, that of vaginitis due to the parasite *Trichomonas vaginalis*. This relatively common and distressing condition, so prone to relapse, often coexists with gonorrhoea. The discharge should be inoculated into Stuart's transport medium and delivered to the laboratory as soon as possible. Smear preparations have not proved to be satisfactory in my hands and therefore are not recommended.

Finally, it must be pointed out that the importance of routine blood tests for all antenatal patients should not be overlooked. A recent investigation carried out in London showed that out of a total of 6,809 antenatal patients 44 (0.64%) were found to have positive Wassermann reactions. There should be little objection to this procedure, as serological tests for venereal diseases can be carried out with the same specimen as that used for Rh grouping.

Next article on Clinical Pathology.—"Tests of Thyroid Function," by Dr. Russell Fraser.

Reports of Societies

LOCAL MEDICAL SOCIETIES

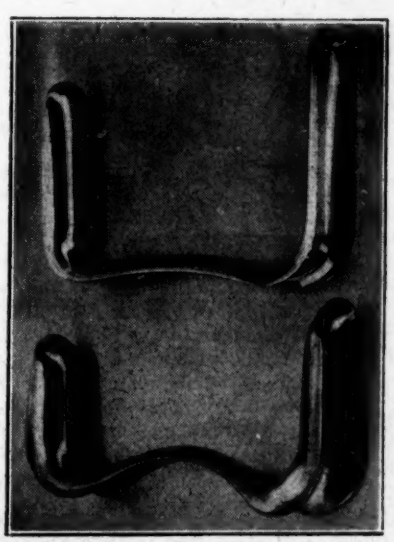
Liverpool Medical Institution

Speaking at a symposium on mitral disease held on February 11 at the Liverpool Medical Institution, Mr. F. Ronald Edwards said that the danger of recurrent rheumatic fever after valvotomy for mitral stenosis had been exaggerated. However, if any considerable mitral regurgitation was present before operation valvotomy appeared to be of little value. Mild aortic stenosis and regurgitation did not contraindicate mitral valvotomy unless the regurgitation was causing lowering of the systemic diastolic pressure. Neither was auricular fibrillation a contraindication to operation, although these cases had a higher mortality. Valvotomy in pregnancy should be undertaken only if the previous obstetrical history indicated it, and then it should be done early. The other contributors to the symposium were Dr. Ronald Ellis, on the medical aspects, and Dr. R. J. Keating, who spoke on radiological diagnosis.

Preparations and Appliances

ST. GEORGE'S MODIFICATION OF SIMS'S VAGINAL SPECULUM

Mr. IAN A. DONALDSON, first assistant, Department of Obstetrics and Gynaecology, St. George's Hospital, writes: A disadvantage of the standard Sims's duckbill vaginal speculum is the relatively short blade, which makes demonstration of the cervix in some patients difficult. The sister of the gynaecological ward at St. George's Hospital designed a modified speculum which has been made by Messrs. Charles F. Thackray Ltd., who have supplied the following technical information about the new speculum.



The whole instrument is shaped from thin material to reduce the total weight, and the overall dimensions of the two blades are: larger blade, 4½ in. (12 cm.) long and 1 1/16 in. (3 cm.) wide; smaller blade, 4¼ in. (10.8 cm.) long and 1¼ in. (2.9 cm.) wide. Varying sizes of the modified speculum have been made. The longer and narrower blades and the marked decrease in weight make them far more convenient to use. The accompanying illustration of the largest examples of the specula shows the difference in dimensions.

Correspondence

Diagnosis of Thyrotoxicosis

SIR,—Professor E. J. Wayne, reviewing various methods of assessing thyroid function in his Bradshaw Lecture (*Journal*, February 20, p. 411), refers to the determination of the serum creatine level in such terms as to give the impression that this test has little diagnostic value; this impression is reinforced in the leading article on toxic goitre in the same issue (p. 443). I should like to state that this view is contrary to the experience of my colleagues and myself in more than 400 patients originally diagnosed on clinical grounds as suffering from some form of hyperthyroidism, and to answer the criticisms levelled at the test.

A normal fasting serum creatine level of less than 0.6 mg. per 100 ml., in both men and women, excludes all but the mildest, relatively symptomless, cases of hyperthyroidism and differentiates sharply the anxiety states from true thyroid disorders. A serum creatine in excess of this upper normal limit, if it occurs in association with the signs and symptoms of hyperthyroidism, though not necessarily with a raised B.M.R., is convincing evidence of thyroid disease; if the B.M.R. is also increased the diagnosis is, in my opinion, beyond doubt. When, as may sometimes happen, especially if the B.M.R. is within normal limits, the diagnosis remains uncertain notwithstanding hypercreatinaemia, a therapeutic test with Lugol's iodine or thiouracil, given for a few days, will result in a fall in the serum creatine if the increase is due to thyroid dysfunction; other forms of hypercreatinaemia remain unaffected.

The method is as clear-cut as is possible with tests of this kind, and the features of other diseases in which the metabolism and serum creatine are raised are sufficiently distinctive to obviate confusion. Contrary to Professor Wayne's statement, overlap of the creatine levels between normal and thyrotoxic men rarely, if ever, occurs; that some apparently normal women may exhibit hypercreatinaemia does not detract from the value of the test if the situation is intelligently assessed and a therapeutic trial performed. Peters's[1] method of estimation is capable of a high degree of accuracy given a good photo-electric absorptiometer and using cells of 2 cm. depth; it seems to be immaterial whether all the substance estimated is creatine or not.—I am, etc.,

London, S.E.1. W. J. GRIFFITHS.

REFERENCE

[1] *J. biol. Chem.*, 1942, 146, 179.

Weber–Christian Disease

SIR,—As Dr. H. R. F. Macdonald reports (*Journal*, February 13, p. 377), the Weber–Christian disease is not very commonly encountered.

I should like to mention two patients because of the apparent effect of treatment. The first, a woman of 50, married and at the menopause, suffered from typical recurring lesions, mostly on buttocks and thighs and ocasionally breasts, over a period of seven years. Several lesions had been excised by a surgeon and the histology was typical. The administration of diphenhydramine hydrochloride, 50 mg. three times a day, cleared the affection within a few days, and there has been no relapse now after three years. The second patient, a female aged 44, had numerous characteristic lesions, mostly over the abdominal wall and breast and occasionally elsewhere, of about six months' duration. The condition was thought by a physician possibly to be leukaemia, but removal of a nodule showed the characteristic picture. This patient was put on promethazine hydrochloride, 25 mg. nightly, and on diphenhydramine hydrochloride, 50 mg. three times a day, while in hospital for a week. On discharge from hospital the promethazine hydrochloride was continued for several months with some slight improvement but no marked clearance. The administration of cortisone, 25 mg. by mouth four times a day for three weeks, cleared the affection in this period, and there has been no relapse after nearly 12 months.

The results in these isolated cases may be no more than coincidental, but it will be interesting to hear the experience of others.—I am, etc.,

Leeds. JOHN T. INGRAM.

SIR,—Like most G.P.s, I tend to become fuddled by the rarities that succeed each other in your columns, but the memorandum on Weber–Christian disease (*Journal*, February 13, p. 377) has solved a five-year-old headache for me.

A cheerful, healthy, obese housewife, then aged 42, developed painful nodules in the legs in November, 1948. She was febrile (→102°) for three weeks, and there was considerable constitutional upset. Indurated swellings, some as large as bantam's eggs, continued to develop in the subcutaneous tissues of the extremities as far up as the deltoids and buttocks. There was no suppuration. Courses of penicillin and sulphadiazine had no effect. At the end of this time she spent a fortnight in hospital, but nothing significant was discovered. She was now afebrile, and slowly resumed her normal life, but further swellings developed in decreasing numbers every few weeks. In February, 1950, she had a typical lesion in the right breast, the only one to occur on the trunk. In June, 1950, she had a cholecystectomy for multiple stones; this had no influence on her other condition—large, usually solitary nodes appearing at slowly lengthening intervals. On February 5, 1954, she presented herself with one about 5 cm. in diameter on the left calf: previous specimens had been negative, but I decided to send one more for culture. Incision produced blood, and curious amorphous yellow globules.

On February 13 I read your memorandum and telephoned Dr. S. Faulds at the Cumberland Infirmary, to whom, and to his colleagues at the pathological laboratory, I am most grateful for the following report, which seems to clinch the diagnosis: "Wet films show large numbers of fat globules and occasional macrophages. This would fit with Weber–Christian disease as you suggested."—I am, etc.,

Appleby, Westmorland. PETER DELAP.

Lilliputian Hallucinations

SIR,—Dr. J. Todd's account of Lilliputian hallucination in a case of trichlorethylene poisoning (*Journal*, February 20, p. 439) recalls to my mind two cases of methyl bromide poisoning in which similar phenomena appeared. One was a youth of 17 with mild symptoms who complained of his feet looking very small, and as if they were a long distance away; his environment was unaffected. The other was a severe case, with epileptiform convulsions, in a man of 25. The ward appeared of normal proportions, but the nurses were horizontal. When later on they appeared to assume the vertical position they were less than half their normal size but "fat and squashed, as if you saw them in a mirror at a fun-fair." Visitors had the same appearance and gave him considerable amusement. He recognized the nurses afterwards as the same people who had appeared in caricature. Inquiries of several other patients with the same condition led to the conclusion that microptic phenomena are uncommon features of methyl bromide poisoning.—I am, etc.,

Hornchurch, Essex. H. WYERS.

Controlled Hypothermia

SIR,—It is pleasant in controversy to find grounds for agreement, and we would certainly support Dr. H. C. Churchill-Davidson's plea for simplicity (*Journal*, March 6, p. 583); not, however, at the price of accuracy. That a general anaesthetic agent may interfere with the thermoregulatory mechanism is unquestioned, but the dose required reduces the patient to a state of deep anaesthesia in which depression of this autonomic function is accom-

panied by depression of every other function, nervous, cardiovascular, and metabolism.

We must insist that thermo-regulation is an autonomic activity. Therefore, if chlorpromazine, or any other drug, proves to have a *predominant* action on the central synaptic connexions of the autonomic nervous system, including those associated with thermo-regulation and vasomotor tone, for the sake of accuracy, and ultimately of simplicity also, it should be described as producing "central autonomic block." It will then be clearly differentiated from the peripheral acting "autonomic ganglion blocking drug." After all, the general anaesthetics produce widespread muscular relaxation, but that does not invalidate the term "relaxant drug" for substances such as tubocurarine.—We are, etc.,

JOHN W. DUNDEE. P. R. MESHAM.
T. CECIL GRAY. W. E. B. SCOTT.

Liverpool, 7.

Anaesthesia in Out-patient Departments

SIR,—In your leading article (*Journal*, February 27, p. 505) you did not bring out clearly what I sought to show at the Royal Society of Medicine. You said that I drew attention to the low potency of nitrous oxide, which was well known, and to the hazards that may follow attempts to obtain "more than light anaesthesia" with it. "*Even* light anaesthesia" would have been nearer the mark, for I showed that, of an unselected sample of adults, less than half could be anaesthetized at all without anoxia, sometimes gross; and I contended that when a "gas" was given the main agent of anaesthesia was, in fact, not nitrous oxide but anoxia—a contention which, in the discussion that followed, was not challenged. In assessing danger, therefore, it is with anoxia, used as an agent of anaesthesia, that cyclopropane has to be compared.

It is true that with cyclopropane there is a risk of explosion which must be constantly borne in mind. But with ordinary care and with the anti-static rubber now available explosions should not occur. But the notion, commonly held, that I wish most to dispel is that cyclopropane is dangerous because it is a powerful anaesthetic. "Overdose" and "respiratory arrest" seem to spring to the mind of anyone who considers its use in the out-patient department. Whilst with nitrous oxide, because of its inevitable anoxia, these are an ever-present menace, with cyclopropane they are far distant and not, in practice, encountered. It is, in fact, precisely because of its power, which enables it to be used throughout with 50% or more oxygen, that cyclopropane, though not perfect, is probably the safest of all existing anaesthetics to administer easily and effectively to out-patients.—I am, etc.,

London, S.E.1. J. G. BOURNE.

Dental Anaesthetics

SIR,—In a paper recently read before the Anaesthetic Section of the Royal Society of Medicine (*Journal*, February 20, p. 452) Dr. J. G. Bourne advocates the use of cyclopropane in dental anaesthesia. During the discussion that followed, attention was drawn to the possible danger of explosion when using this gas. That this is no mere theoretical objection is well borne out by the following incident which may be of interest to any of your readers who may contemplate trying out the suggested mixture of cyclopropane–oxygen.

A short time ago a dental colleague was engaged in a rather difficult extraction on a patient under nitrous oxide anaesthesia. The forceps accidentally slipped from the tooth, giving rise to a shower of sparks, which, in spite of a well-lit surgery, was plainly visible to myself and the nurse in attendance. Had I been using cyclopropane I am afraid that the result might have been very unpleasant for all concerned.—I am, etc.,

Hove. H. NEWTON-ANDREWS.

Methylpentynol

SIR,—I was interested to read Dr. A. G. Boag's letter in which he draws attention to the use of methylpentynol for premedication (*Journal*, February 13, p. 393). In addition to the ward procedures that he mentions, I have found this drug of value in allaying anxiety before the administration of a barium enema. Radiological examination is facilitated by the patient's fuller co-operation.

Methylpentynol also seems to be helpful in attacks of asthma. It may be given four-hourly in doses of 0.5 to 1.0 grammes as long as an attack lasts. The reduction of anxiety permits a better response to the usual treatment.

May and Ebaugh[1] reported very favourable results from the use of methylpentynol as a sedative in aged patients. There is no completely satisfactory sedative for such patients and it is well known that barbiturates may induce or increase mental confusion and restlessness. Methylpentynol seems to be effective in certain cases and has advantages over paraldehyde, which is more commonly given. The dose used must often be large. As your annotation (*Journal*, August 22, 1953, p. 435) states, there is no analgesic action in methylpentynol and probably it fails to act in those elderly persons whose insomnia and restlessness are dependent on physical discomfort or pain. Nevertheless, the drug is worthy of further assessment, especially in patients with cerebral arteriosclerosis.—I am, etc.,

London, N.9. A. N. EXTON-SMITH.

REFERENCE

[1] *J. Amer. med. Ass.*, 1953, **152**, 801.

SIR,—I share Dr. A. G. Boag's interest in methylpentynol (*Journal*, February 13, p. 393), as I myself am testing this as premedication for children having tonsillectomy. It is my wish to find a drug with qualities that include production of sleep so that the children know nothing of their visit to the theatre, simplicity and acceptability of administration, minimal depression and cough reflex and respiration, no vomiting, and no post-operative restlessness. Quinal barbitone ("seconal") and pentobarbitone ("nembutal"), of which I have considerable experience, were less than perfect in the fifth of these requirements; rectal thiopentone in the second.

Till now I have used methylpentynol for 62 cases, and have found the requirements generally satisfied except for failure to produce sleep. Instead, however, the children, almost without exception, have arrived in the anaesthetic room calm, quiet, happy and co-operative, and sometimes sleepy. It has proved wise to give the elixir one to one and a half hours pre-operatively in a dosage of 500 to 750 mg. Even so, it is unlikely to be sufficient premedication for undisciplined children and those who are frightened of hospitals. Results with methylpentynol appear so encouraging as to warrant completion of the investigation.—I am, etc.,

London, W.10. CHRISTINE M. RENDELL.

Cortisone and Manipulation of Knee-joint

SIR,—The report entitled "A Comparison of Cortisone and Codeine Medication as an Adjuvant to Manipulation in Rheumatoid Arthritis" (*Journal*, January 30, p. 233) demonstrates an immense amount of careful work, especially in co-ordination between groups as widely separated as Bath, Sheffield, and the London area. The administration involved to produce this report must have been considerable. But what has it achieved? In the summary to this report it is stated, "A controlled trial has been made of the value of cortisone as a cover to manipulation of the knee-joint in patients with rheumatoid arthritis. . . . In the dosage given there was no evidence that cortisone was in any way superior to tab. codein. co. for the purpose at issue." Yes, certainly, there is much ground for their actual findings, and negative findings are often of real value. Apart from this, my impression on first reading this report was to answer my question by an emphatic "Exactly nothing." But on my second and third reading other thoughts came to me that are, I trust, worthy of consideration.

The first of these is to note that the graph (unnumbered) at the top of page 235 shows steady improvement during the pre-therapy period, rudely interrupted by the treatment, and then further days elapse before the curve initiated during the pre-therapy period resumes its quiet progress. This point can be seen readily by casting the eye across the gap caused by "the trauma of this operation." My second is to note with interest from Table V of the "contralateral knee-joints (non-manipulated)," that the pain, range of movement, and timing tests all show a nearly smooth curve of improvement—thanks probably to a combination of hospitalization, enforced rest, and by "every endeavour was made to get the patient walking as early as possible."

Now I come to two quite different thoughts. It is stated: "In a proportion of cases these contractures cannot be corrected by conservative methods, and manipulation under a general anaesthetic is required." What evidence does this paper produce for the clinical accuracy of this *ex cathedra* statement? Absolutely none. Again, there is no description of the method or extent of the manipulation. Anyone with the smallest experience of manipulating joints in active cases of rheumatoid arthritis, such as those treated in this survey, knows that the technique is critical. Indeed there are many physicians and surgeons who would hesitate to manipulate (presumably under an anaesthetic, though this is not stated) a knee in a patient whose E.S.R. averaged 20 mm. Since when has it been a good form of therapy in joint disease cases to subject an actively ill patient to a form of therapy that increases their pain and diminishes their mobility as shown by the authors' graph?

Is it not time that a halt was called to these so-called methods of research, where every care is taken to leave no loophole for criticism of the methods employed or the deductions made? To cease, also, this unnatural way of regarding patients as so many pieces of machinery or guinea-pigs, and return to those methods of simple clinical judgment and observation where results are gauged by the method of presentation and by the individual's reputation for accurate and humane genuine medicine. Harvey, Lister, Mackenzie, Banting, Fleming, and many others secured the real advances that stand for ever to their credit by the very individuality of their work.—I am, etc.,

Chipping Campden. C. B. HEALD.

Changes in Skin Response in Asthma

SIR,—I have read with great interest Dr. A. G. Ogilvie's article on changes in skin response in asthma (*Journal*, February 13, p. 370). These variations have for long been recognized, but have been all too little discussed.

A positive skin response merely demonstrates that specific antibody is present either in the epidermal cells or in the blood contained in the capillary loops. It is probably true that specific antibodies can at times be concentrated in other tissues—e.g., the bronchial or gastric mucosa—without being present in either skin or blood, in which case there will be no "immediate" weal and flare reaction when the sensitizing agent is applied to the skin. Conversely, it is well recognized that some patients give positive skin reactions to allergens with which they are no longer in contact, and which therefore cannot be the present cause of their attacks. In such cases the causative factor or factors must be sought elsewhere, and they may be found to be other than allergic. For these reasons I think that it is unsound to accept positive skin reactions as the criterion of a dominant allergic aetiology, without reference to the history, environment, and physical examination of the patient.

A number of diverse factors—hormonal, psychogenic, infective, for instance—can affect the concentration of antibodies, and therefore the intensity of the skin reaction. Dr. Ogilvie found that all his cases that had been "desensitized" gave negative reactions at the end of their courses of injections. This is a common finding, and is presumably due to the production of a blocking or inhibitory antibody. With regard to the development of fresh sensitivities, one has often found this to occur, sometimes dramatically. It has usually been demonstrated in the course of a reinvestigation when a case has relapsed. There are therefore several comprehensive reasons why there may be variations in the skin reactions in the same patient over a number of years, and I quite agree with Dr. Ogilvie that it is futile to attempt to assess clinical progress solely on the basis of these reactions without consideration of the case as a whole.

Nevertheless, skin testing is a procedure without which it is impossible to make an adequate aetiological diagnosis in the majority of cases of asthma. It should, of course, be properly carried out by an experienced person, with negative and positive controls, using extracts of individual allergens (rather than groups) of known concentration and of reliable origin.—I am, etc.,

York. HAROLD ROYLE.

SIR,—Dr. A. G. Ogilvie's observations in his paper on "Changes in Skin Response in Asthma" (*Journal*, February 13, p. 370) are so much at variance with general experience that an attempt must be made to explain them. I should like to comment under the following headings.

Technique of Testing.—The technique of skin-testing has now been more or less standardized for many years. The quantity of extract usually injected in the intradermal method is 0.01–0.02 ml., just five to ten times less than the amount injected by Dr. Ogilvie. The disadvantage of using relatively large volumes of extract is well recognized. I quote from two well-known textbooks. Cooke[1] states: "The common practice of injecting as much as 0.05 to 0.1 ml. in the performance of an intracutaneous test should be condemned. The initial trauma resulting from the injection of such a large amount of fluid into the skin is sufficient to produce non-specific wealing. This is not only misleading in itself but impairs the diagnostic value of many tests which produce only slightly positive reactions but which, nevertheless, are specific and of diagnostic significance." Vaughan and Black,[2] in discussing the technique of the intradermal test, say, ". . . Then press on the plunger introducing 0.01 or 0.02 cc. of the extract into the epidermal layer."

It is small wonder that many of Dr. Ogilvie's patients quailed at the thought of a second assault by his "energetic young skin-testers," and he may be accounted fortunate that this procedure was not followed by any serious results. A number of deaths have been recorded following skin tests with smaller quantities of extract than he employed. Presumably, the frequency of false positive reactions obtained by this technique explains his criterion for a positive reaction—namely, "a definite weal of at least the size of a silver threepenny-piece with pseudopodial irregularities and surrounding erythema." This would exclude many significant reactions and would explain why he has been unable to confirm sensitization in patients with strongly positive histories. It would also probably account for the apparent change from negative to positive and vice versa, when patients were retested after several years: many of those considered negative were probably still positive but not up to threepenny-bit standard—in other words the responses may have varied in degree rather than changed from positive to negative or negative to positive.

Variation in Potency of Extracts.—Dr. Ogilvie does not state whether fresh extracts were used from time to time, but, since the potency of few, except perhaps the pollens, would have remained unaltered during the time of his investigations, one assumes that he has done so. Unfortunately, we still have only rough methods of standardizing our extracts so that no two preparations made at different times can be regarded as identical in potency or quality. This applies especially to mixtures of extracts as used for "group testing." I habitually employ commercial extracts and find that they vary considerably in potency: this is not a reflection on the firms who put them up but an indication of the crudity of our methods of preparing extracts. I am at present using an extract of cat hair which gives a high proportion of positive reactions, many of which cannot be justified from the history: a short time ago the cat hair extract from the same firm rarely caused reactions. In other words, a change in the extract rather than a change in the patient may account for some of Dr. Ogilvie's observations.

Site of Test.—The site at which skin tests are carried out is important: if the forearms are used larger reactions are obtained near the bend of the elbow and smaller ones near the wrist using the same amount of the same extract. If the arm was in fact employed as the testing site, were precautions taken to ensure that the same relative positions were used for each test substance at the time of the original and subsequent tests?

Effect of Drugs.—Dr. Ogilvie does not state if precautions were taken to ensure that drugs such as adrenaline, ephedrine, or antihistamines were not taken on the day the tests were carried out. These drugs are well known to cause reductions in skin sensitivity.

My own observations[3] have shown a remarkable consistency in the skin responses of a small group of pollen-

sensitive patients tested repeatedly over three years. The reactions invariably diminished immediately after treatment and when the scratch test was employed sometimes disappeared, but they had almost returned to the pre-treatment level four months later: there was little variation from year to year. No one would deny that changes in skin responses do occur sometimes apparently "inconsequentially"—new sensitivities develop and old sensitivities fade away. Like Dr. Ogilvie, I have always been sceptical of the value of skin-tests, but in investigating their vagaries one must stick to the rules. The really odd thing about his paper is his final comment (with which I am in full agreement) that "skin-testing . . . in the individual case may give valuable information if used with discretion."—I am, etc.,

London, W.1. R. S. BRUCE PEARSON.

REFERENCES

1 *Allergy in Theory and Practice*, 1947, p. 501. Philadelphia and London.
2 *Practice of Allergy*, 1948, p. 184. St. Louis.
3 *Guy's Hosp. Rep.*, 1940, 90, 65.

The Prevention of Pulmonary Embolism

SIR,—Your annotation on pulmonary embolism (*Journal*, January 23, p. 202) prompts me to report a method designed to prevent this post-operative complication.

At the conclusion of the operation the surgeon and his assistant raise the patient's legs through an angle of 80 degrees. The powdered palm of the hand is then used to massage the patient's calves from the tendo achillis to the popliteal fossa. The patient's feet are then passively flexed and extended at the ankle. The legs are lowered on to an inclined plane of 45 degrees, which is placed on the stretcher canvas on the operating table; the tendo achillis rests on a sorbo-rubber bridge—a rubber loop fixed to the top of the inclined plane is slipped over the feet to prevent the legs from rolling off. When the patient is returned to bed the legs are kept at an angle of 45 degrees by a wider inclined plane which is slipped in under the mattress until active toe and foot movements are possible.

This treatment is based on the belief that most cases of post-operative pulmonary embolism result from clots which have their origin in the veins of the calf, and which begin to form during and shortly after operation; although the coagulability of the blood is altered, the venous stasis and endothelial trauma are all-important. By making use of gravity, massage, and the venous pumping action of the calf muscles it is ensured that no early thrombotic changes occur in the veins of the lower limbs before the patient regains consciousness, after which active toe and foot movements are possible.

The writer has been impressed with the incidence of pulmonary embolism among patients who have been in bed for any length of time pre-operatively, and, although it is not intended to list other prophylactic measures in general use, the precaution of keeping patients who are admitted to hospital for pre-operative treatment or investigation ambulant, whenever possible, will bear repetition. In passing, it may be mentioned that following operations in the lithotomy position, particularly in middle-aged and more elderly patients with atheromatous changes in the cerebral vessels and in whom a sudden lowering of blood pressure predisposes to cerebral thrombosis, and following obstetric operations in the lithotomy position when a lowering of the legs to the horizontal is not immediately desirable, the inclined plane has proved its value.

In conclusion, Sir, this simple piece of apparatus will help to reduce the incidence of post-operative venous thrombosis and its sequelae, and the complications resulting from a sudden fall in blood pressure, and will later form the subject of a more detailed communication.—I am, etc.,

Chelmsford. ANTHONY PEARSON.

International Nomenclature for ABO Groups

SIR,—Before the adoption of the international nomenclature for the ABO groups, considerable confusion between the British and Continental literature occurred between groups I and IV as a result of using Moss and Jansky terms respectively. It was hoped that the international notation would avoid all future errors; nevertheless, this has not proved to be the case. Before the international terms were instituted sera for grouping were issued as II and III, whereas for a time after the inception of ABO, the sera issued were labelled A and B. Some time ago the labels on sera for grouping were altered to anti-A and anti-B, the contents of which were respectively B and A, an apparent reversal to the uninitiated. Why this change took place, apparently without international agreement, is not clear.

Arising out of this change we have recently had a young house officer who previously held an appointment in the U.S.A., where, she stated, the previous method of labelling—that is, A and B—continues. One night recently, as an emergency, she grouped a patient preparatory to blood transfusion, and made the group B instead of A as a result of the labelling anti-A and anti-B. It was entirely new to her, and she had not seen this notation before. The mistake was corrected in time to avoid any possible transfusion disaster. Surely, however, the whole circumstance raises an important question of principle; the labelling of material of this kind should be a matter of international agreement. This will avoid confusion in the literature and, further, avoid possible disasters to patients. It seems to me to be entirely wrong that any change of nomenclature should be permitted unilaterally in one country. In short, an international agreement, once accepted, must not be broken by any individual country without due notice to all affected by such a decision.—I am, etc.,

London, S.E.18. W. SMITH.

Improved Hearing by Re-education

SIR,—I feel it important that everyone interested in deafness, and especially otologists, general practitioners, and the lay hard-of-hearing public, should be careful about accepting unreservedly the claims made for improved hearing by re-education methods without hearing-aids. The claim is made concerning persons ranging from the hard-of-hearing (but not requiring an aid) to those with marked high-tone deafness, and even for some too deaf for an aid to help at all. An increase of ability to listen is denied; it is considered a definite improvement by releasing "latent" hearing. This may be so, but the principle needs medical and scientific investigation before the practice is recognized as of true value.

At present, the sponsors assess improvements only with a "live" voice and uncalibrated "complex" sound tests; any change in pure-tone audiometry is disclaimed and speech audiometry is not used. The value of the gain in hearing is also gauged by letters from grateful patients and clients, which, though enlightening, are in fact unscientific evidence and all too reminiscent of advertisements for patent medicines or "cures" in the Hunterian era.—I am, etc.,

London, W.1. IAN G. ROBIN.

Atelectasis as a Complication in Artificial Pneumothorax

SIR,—In the first paragraph of Dr. R. L. Sadler's article on atelectasis as a complication of artificial pneumothorax (*Journal*, February 13, p. 359) we read: ". . . Some authorities seem to regard it as a dangerous procedure which should be used only in exceptional cases (Harris *et al.*, 1952 . . .)." We are at a loss to understand how Dr. Sadler can interpret anything we wrote in our paper[1] which can even remotely resemble the sentiments he attributes to us. If we may quote a sentence of our paper which appears to be relevant: "We think that the over-all results are good. With better selection, chemotherapy, and thoracoscopy, we believe that the artificial pneumothorax still has an important role to play provided that it is well maintained and that it is looked upon purely as a temporary collapse measure."

Does Dr. Sadler really suggest that he understands from that that we regard an artificial pneumothorax as a dangerous procedure? Even in our review of the literature we quoted no authority to suggest that the procedure was dangerous, although we did suggest that it was losing favour in many centres.—We are, etc.,

W. C. HARRIS.
FAITH C. POLES.
A. W. ANDERSON.

Edgware, Middlesex.

REFERENCE

[1] *Quart. J. Med.*, 1952, 21, 447.

A Naval Occasion

SIR,—I was greatly entertained by your reviewer's reaction to my book *Our National Ill Health Service: An Essay on the Preservation of Health* (*Journal*, February 20, p. 441). Of course it is generally the author's lack of perspicacity if he fails to get a reviewer to follow his thesis. My subject was social health, in which, I tried to explain, I did not include clinical medicine. Therefore I hope you will not mind correcting the suggestion of Dr. Ffrangcon Roberts that the care of social health in the Royal Navy "had to be buttressed by the appointment of civil consultants who were given the rank of [rear] admiral." One is truly grateful to the eminent consultant clinicians who have given their services to the sick and wounded seamen, in peace as well as war. During the war the Navy expanded sevenfold, which, of course, needed a proportionate increase of "doctors" of all sorts. In fairness to the regular naval medical officers, it was not necessary to buttress their health duties by entering a single high rank consultant in social or preventive medicine, or give any "hostilities-only" medical officers of health a relatively higher rank than their permanent colleagues.

I can only cry *Touché* to my slip about the authorship of *Ecclesiastes*. It was deplorable; and not to be excused by the bad old custom of casually attributing all the "wisdom books" of the Hebrew scriptures as a matter of course to Solomon.—I am, etc.,

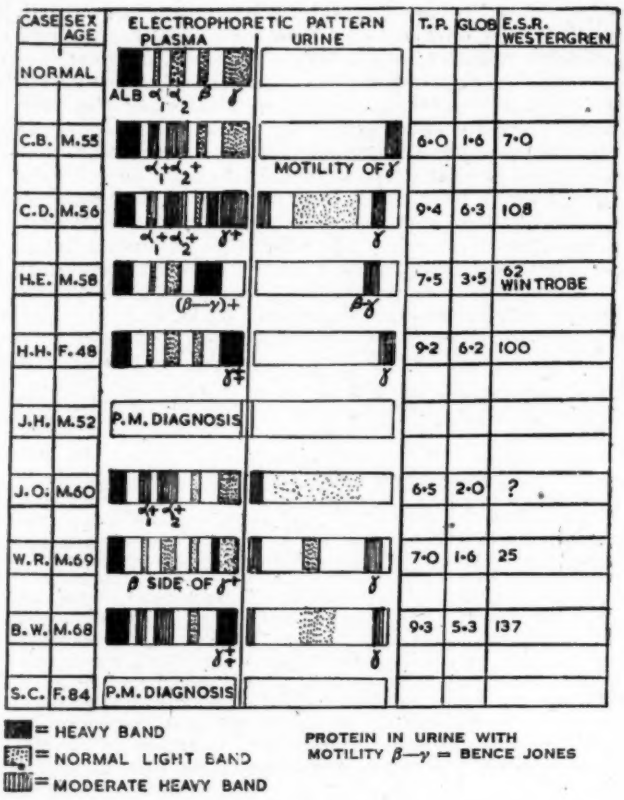
Leamington Spa. SHELDON F. DUDLEY.

Myelomata of Bone

SIR,—With reference to the article by Mr. A. Naylor and Dr. F. E. Chester-Williams (*Journal*, January 16, p. 120) I should like to make some observations about the use of electrophoresis in demonstrating abnormal proteins in serum or urine.

In the past seven months at Kingston Group Laboratory, eight cases of multiple myelomatosis have been diagnosed by pathological investigations, and the part shown by electrophoresis of serum and urine is shown by the following chart. Dr. K. G. Cuming of this laboratory has confirmed some of these cases by marrow puncture and Dr. J. C. Lees by necropsy and tissue section. Although for final and undisputed diagnosis several criteria are necessary, those of first importance during life are positive marrow biopsy and the demonstration of an "abnormal" globulin in the blood or urine. The cases show that where an "abnormal" protein is not present in the serum it may be demonstrated in the urine. (I am indebted to Dr. F. V. Flynn, of University College Hospital, for urine electrophoresis in some of these cases). The case of J.O. suggests that in spite of the presence of a small round-celled solitary neoplasm of the femur, the failure to demonstrate "abnormal" proteins indicates that plasma cell myelomatosis is unlikely.

Since electrophoresis is an easy laboratory technique it would be important to know if cases exist of proved plasma cell myelomatosis where no protein abnormality can be demonstrated by this method. There is no doubt that electrophoresis may demonstrate what may be called false positives, since there has been one case in this hospital where a typical γ-globulin band has been seen with no other evidence of myelomatosis. The three-tube heating test for Bence Jones protein in urine has been demonstrated to be inadequate in the above cases, especially in the hands of



more junior technicians. In no case has the test been absolutely typical of the text-book criteria—e.g., disappearance above 80° C. and reappearance on cooling. I would suggest that urine electrophoresis should always be done in cases of proteinuria and anaemia with back or leg pain over the age of 40 if cases of myelomatosis are not to be missed. Even the mode of death, sometimes in uraemia, does not necessarily suggest marrow dyscrasia.

The excretion of these abnormal globulins is interesting in relation to Professor Squire's recent article on protein excretion and reabsorption in the normal kidney. What is the normal method of metabolizing and excreting the very large γ-globulin molecule? The relation of plasma cells to globulin antibodies may be investigated in these cases of myelomatosis, since it can be demonstrated that several different globulins of different electric charge and molecular size are formed. The so-called neoplastic cells seem to form abnormal substances, but it is possible that an excess may accumulate (or be excreted) in response to an unusual antigen, or because of failure in the normal metabolism and excretion. With these new methods of diagnosis more cases of plasma cell multiple myelomatosis are found, and it can no longer be considered to be a rare disease.—I am, etc.,

Kingston-on-Thames. PHYLLIS DAGNALL.

Press Publicity

SIR,—As a public representative I have been very interested in the letters and comments in your columns on the subject of press publicity about the Health Service. It is unfortunate that some persons in authority still fail to appreciate that the Service belongs to the community and that ordinary citizens are entitled to know all about its progress and problems. The attitude of "Theirs not to reason why" dies hard, and it remains a cause of deep resentment to intelligent citizens wherever they come in contact with it.

The average layman is certainly reluctant to complain about or to experts with professional qualifications. He is not quite so reluctant to complain to his Member of Parliament. A study of Parliamentary Questions and of M.P.s' correspondence would, I know, reveal numerous ex-

amples of the failure of boards, councils, and committees to let the public know what they are doing and why. By neglecting the regular supply of information, such authorities not only create suspicion and mistrust but lose the potentially powerful support of public opinion for the greater funds and resources they often need.

It is in the interests of all who work in the Service, as much as of those who require its facilities, that every citizen should feel a full sense of responsibility for its efficiency. But this relationship cannot develop unless the administrative and medical powers-that-be take the public into their confidence, stop being secretive about their decisions, and start inviting consumers to offer their suggestions for improvements and reforms. The best are doing this already, and I am confident that all who have tried this approach have found that there is a substantial fund of goodwill for the Health Service on which to draw.—I am, etc.,

House of Commons, S.W.1. STEPHEN SWINGLER.

Infant B.C.G. Vaccination

SIR,—Dr. H. M. Purser's account of 2,500 B.C.G. vaccinations in newborn infants (*Journal*, February 13, p. 368) is of special interest in view of the exclusion of this age group mentioned in Memorandum 324/B.C.G., British Ministry of Health, November 5, 1953). As B.C.G. vaccination has been part of the Local Authority Anti-tuberculosis Service in Dublin since October, 1948, and 4,507 newborn infants have been vaccinated here, perhaps we may be permitted to comment on our experience.

When our scheme commenced attention was concentrated on contacts. From study of the annual childhood tuberculosis mortality in Dublin, we realized that children under 5 years of age had the highest mortality. For this reason it was decided to make B.C.G. vaccination available for all infants born in the maternity hospitals irrespective of contact. By kind permission of the Master of the Rotunda and Dr. W. R. F. Collis, paediatrician, the scheme for B.C.G. vaccination of the newborn began at the end of September, 1950. The scheme was later extended to the Coombe Maternity Hospital with the kind consent of the Master and Dr. W. Kidney, paediatrician, and each month has shown an increase of the number of vaccinations. Dr. Purser has raised the question of congenital tuberculosis, and we agree that a pre-vaccinal test is desirable if the mother is an open case, otherwise we dispense with pre-vaccinal testing in newborn infants.

We have not used the double dose of vaccine in infants—we use the same technique and method of administration as in the older age group. We subdivide 0.1 ml. of Danish vaccine into three intradermal injections made slightly apart over the middle of the left deltoid. The subdivision of the dose minimizes the risks of ulceration and adenitis. Dr. Purser refers to multiple adenitis. It is not clear if these occurred in both axillae as a result of both deltoid areas being used. This appears to be one of the disadvantages of the double dosage. The incidence of axillary adenitis and abscesses is somewhat less in our series using the single dose technique.

Incidence of Regional Adenitis—Comparison Belfast and Dublin

	Total Vaccinations New-borns	Total Regional Adenitis	Simple Adenitis	Abscesses
Belfast ..	2,500	46 (1·84%)	28 (1·2%)	18 (0·72%)
Dublin ..	3,429	52 (1·51%)	31 (0·9%)	21 (0·61%)

The above Dublin figures relate to vaccinations completed to the end of June, 1953, as complications occurring in vaccinations carried out since July, 1953, may not show until 1954. Many cases of adenitis do not appear until six to nine months following vaccination. The complication figures in the above table are at variance with those reported by Gaisford and Griffiths,[1] who reported 50 abscesses in 1,461 vaccinations—i.e., 3.4%. These workers used two different vaccines, and varied the dose with the object of expediting the conversion time. Many of their vaccinations were made in the buttock—we have avoided the use of the napkin area, and our invariable site of injection is into the skin over the left deltoid.

Dr. Purser has omitted to state what post-vaccinal tests were used, and at what time tests were applied by the practitioners on infants domiciled outside Belfast City area. In Dublin we prefer to use a post-vaccinal Mantoux of 0.002 purified protein derivative in infants. Jelly or ointment tests are liable to be washed off, and, due to the sensitivity of the skin of infants, erythema without papules may give rise to misleading results when read by various readers. We find that the conversion rate depends on the time allowed to elapse between vaccination and post-vaccinal tests. A number of mothers fail to bring their infants in eight weeks' time for these tests. This entails much follow-up work, but has the advantage that the longer the delay to do post-vaccinal testing the better the conversion rate. We agree with Dr. Purser's findings on annual tests. In a random sample of 203 annual tests of newborn infants vaccinated prior to 1952 only one had become negative, so it would appear better to retest at school entry.

In this total of 4,507 vaccinations in Dublin and 2,500 in Belfast, little of the distressing complications envisaged in Memorandum 324/B.C.G. have appeared. Because of the conflicting attitudes to B.C.G. vaccination of newborn infants and the rarity of reports in the literature, Dr. Purser's article is worthy of study.—I am, etc.,

Dublin. M. DUNLEVY.

REFERENCE

[1] *British Medical Journal*, 1951, 2, 702.

Prolonged Hypotension Following Hibernation Anaesthesia

SIR,—The papers in the *Journal* of December 5, 1953, by Dundee, Gray, *et al.* (pp. 1237 and 1244), and Smith and Pairer (p. 1247) have been most interesting and stimulating. One of the complications of hibernation anaesthesia not mentioned by either groups has been that of "failure to rewarm," as discussed by Huguenard.[1] This complication, he states, is commoner in the older patient. One of the associated features of failure to rewarm may be that of prolonged and possibly progressive hypotension. We should like to quote the following case as an example.

A female of 78 years, weighing 120 lb. (56.3 kg.), was admitted to hospital with a closed fracture of the upper third of the shaft of the femur. It was proposed to carry out an open reduction of the fracture with fixation of the fragments by cross-screwing. The patient's condition was fair for a woman of her age. The blood pressure was 150/100 mm. Hg, pulse 100/min., regular in character, haemoglobin 13.5 g.%, and the red cell count 4,320,000 c.mm. The heart sounds were of good quality and the chest clear. Premedication consisted of morphine gr. ¼ (11 m.g.) and atropine gr. 1/100 (0.65 mg.) given one hour before operation. It was decided, however, later to use hibernation technique in this case.

Accordingly, the patient was given 10 ml. over a period of 10 minutes of a mixture of pethidine, 50 mg., promethazine, 25 mg., and chlorpromazine, 25 mg., which had been diluted to 20 ml. in saline. At the end of 10 minutes the patient was asleep and she was intubated with ease. She was then given a mixture of 4 litres of nitrous oxide and 4 litres of oxygen, using a semi-open circuit. At this stage the blood pressure had fallen to 80/45 mm. Hg, and the pulse had risen in rate to 120/min. Bleeding was minimal throughout the operation, despite the fact that severe surgical handling of a difficult fracture took place. In all some 40–50 ml. of blood was lost. The blood pressure and pulse rate remained steady throughout the operation. One hour later at the end of the operation the patient objected to the endotracheal tube as soon as the nitrous oxide–oxygen mixture was withdrawn and the tube was removed and replaced by an ordinary airway.

On return to the ward the blood pressure had fallen to 70/40 mm. Hg, and two hours later, despite elevation of the foot of the bed, to 50/20 mm. Hg, the pulse remaining steady at 120/min. The colour at this stage was not good, the skin being waxy-white in appearance. The ears, however, were quite pink on rubbing and the arteriolar-capillary refill time seemed satisfactory. The respiratory rate and depth seemed adequate at this stage. A clinical thermometer placed in the rectum did not register, the temperature having fallen to under 95° F. (35° C.). As suggested by Huguenard, the intravenous administration of atropine gr. 1/50 (1.3 mg.) followed by neostigmine 5 mg. was carried out without much success. Except for slight fibrillary twitching of the fingers and eyelids, little was observed, and the blood pressure remained at 50/20 mm. Hg and the pulse rate at 120/min. The foot of the bed was now raised to a twenty-degree tilt and hot-water bottles were applied cautiously to the trunk. An intravenous transfusion of 1/250,000 solution of L-*nor*adrenaline was now set up. After a few ml. of this solution

was run in, the blood pressure rose to 120/80 mm. Hg, and the pulse slowed to 80/min. The patient now began to warm slowly and there was a marked return of muscular tone. She answered to her name some 10 hours after her return to the ward and was wide awake in 12 hours. Altogether some two pints (1.1 l.) of the L-*nor*adrenaline solution was given over a 10-hour period. Recovery has been uneventful and the patient is now well, but of course not yet walking due to her orthopaedic condition. The temperature was slow to rise, and after two days was still only 96° F. (35.6° C.) rectally, although she felt well and did not complain of cold.

The administration of atropine and neostigmine, which, according to Laborit,[2] induces the liberation of adrenaline, had little effect in this case. Atropine blocks the cholinergic muscarinic effects, while neostigmine elicits a stimulation of the pre-ganglionic fibres. Recourse therefore had to be taken to supportive adrenergic therapy as hibernation was obviously reaching an irreversible phase.—We are, etc.,

FRANK S. PRESTON.
HUGH Y. WISHART.

Glasgow, W.1.

REFERENCES

1 *Anesthet. Analg.*, 1953, **10**, 16.
2 *Presse méd.*, **59**, 1329.

Utero-tubal Insufflation

SIR,—Despite Dr. A. Sharman's statement ("Some Lessons from 4,000 Utero-tubal Insufflations," *Journal*, January 30, p. 239) that no harm arises from insufflation of the fallopian tubes with carbon dioxide in the pre-menstrual phase of the cycle, it seems likely that more patients will be found to have patent functioning tubes on first investigation if kymography is carried out about mid-cycle or before.

The annotation on this subject (p. 265) repeats the assertion that the variations on insufflation may be due to other factors than tubal patency and motility; all the work of Rubin and Sharman is based on the proven fact that the information obtained is definitely attributable to the fallopian tubes alone, and, if this is not assumed, then our conclusions from kymography at present are based on a false assumption.—I am, etc.,

STANLEY A. BOND.

Cheltenham.

SIR,—Mr. Albert Sharman in his interesting survey of utero-tubal insufflations (*Journal*, January 30, p. 239) refers to the question of failure of passage of the gas resulting from tubal spasm, and describes failure of action of spasmolytic drugs. In this unit we have, for the past three years, used amyl nitrite in all cases where the gas has failed to pass at a pressure of 200 mm. This is administered in the usual way by inhalation from a fractured glass capsule, and in a large proportion of cases has led to relaxation of tubal spasm and the passage of the gas, with subsequent demonstration of normal peristalsis at low pressures. In such cases the use of diphenhydramine before intercourse at mid-cycle has subsequently been recommended and a number of pregnancies have followed.

Amyl nitrite has also been used where difficulty has been encountered in passing a biopsy curette for endometrial biopsy, and in many cases relaxation of cervical spasm has been demonstrated which has enabled the biopsy to be completed. The action of amyl nitrite in these cases is similar to that seen in retained placenta with contraction ring. I would recommend the use of this drug in all cases of apparently negative insufflation, since it may avoid repeated interventions and also the false diagnosis of tube blockage. I may add that we have generally used it without anaesthesia, but that it appears to be equally effective with anaesthesia.—I am, etc.,

J. A. CHALMERS.

Worcester.

The Cerebrospinal Fluid in Diagnosis

SIR,—In his article on the cerebrospinal fluid (*Journal*, February 20, p. 449) Dr. J. N. Cumings has made several statements about the C.S.F. protein which are not supported by modern work.

He states that the protein is almost all albumin with only a trace of globulin. This is not true. Merritt and Fremont-Smith, using chemical methods, found an A:G ratio of about 5:1. They probably measured only the γ globulin present. Kabat *et al.*,[2] using an immunological technique, found a similar value for the albumin:γ globulin ratio. However, Schneider and Wallenius[3] found that cerebrospinal fluid subjected (after concentration by dialysis) to paper electrophoresis gave patterns similar to normal sera with A:G ratios of 1–2:1. Parallel examination of C.S.F. and serum from the same patient showed the protein components of the two to be similar.

Dr. Cumings gives the value of the C.S.F. protein for children as 10–15 mg.%. As long ago as 1928 Stewart,[4] in 50 normal children, found an average value of 35 mg.% (S.D. 11), using a turbidimetric method. Dr. Cumings also gives the normal values for adults as up to 30 mg.%, although he admits that in elderly people values of 50–60 mg.% are sometimes found. Kabat gives a mean for adults of 37 mg.% (S.D. 8), also measured turbidimetrically. It is now well known that all turbidimetric methods are unreliable. When turbidities are read visually against standards, a common method, considerable errors occur sometimes of the order of 50% or more. Greater accuracy is got by using a photo-electric absorptiometer to read the turbidity, but when compared with Kjeldahl protein determinations on the same normal samples, the turbidimetric method gives an answer lower by about 10–20% (Hall, 1954, in press).

During the past five years I have used a biuret method employing a modified Weichselbaum reagent for C.S.F. proteins. The method gives excellent correlation with Kjeldahl determinations. Protein values for adults and children are a little higher than reported by previous workers, the average value being 40–50 mg.%. Values of 60–70 mg.% are not uncommon.—I am, etc.,

M. LUBRAN.

Isleworth, Middx.

REFERENCES

1 *Cerebrospinal Fluid*, 1937, Saunders, Philadelphia.
2 *Amer. J. Med.*, 1948, **4**, 653.
3 *Scand. J. clin. Lab. Invest.*, 1951, **3**, 145.
4 *Arch. Dis. Childh.*, 1928, **3**, 96.

Prevention of Bovine Tuberculosis

SIR,—We were surprised to read Drs. R. W. Kind and M. C. Brough's suggestion (*Journal*, February 13, p. 372) that their cases of bovine tuberculosis emphasize the need "either for ensuring that the milk supply throughout the country must eventually come from accredited tuberculin-tested herds or the general pasteurization of milk." Surely the boiling of milk offers the only certain preventive measure and pasteurization but a reasonably safe alternative. Tuberculin-tested milk carries no guarantee; only in the past few months have we seen a larger but similar outbreak to the one in Leicestershire occur amongst children given milk from an accredited herd, the damage commencing shortly after a routine check of the cows.

We beg to suggest as an immediate preventive measure that, wherever possible, only pasteurized milk be issued to schools. In those instances where this is impractical parents should be notified so that those who wish may make alternative arrangements.—We are, etc.,

T. R. MAURICE.
HUGH ELLIS.

Marlborough.
Oxford.

Depression Treated by E.C.T.

SIR,—I was most interested in the article entitled "Prognosis of Depression Treated by Electric Convulsion Therapy" by Dr. Hugh F. Jarvie (*Journal*, January 16, p. 132), and agree most strongly with his enunciation on the importance of critical assessment of the long-term results of this treatment. From his study of 114 cases of depression, Dr. Jarvie concludes that E.C.T. is an effective form of treatment in most cases of depression, but adds the rider that "its limitations in some 30 to 40% of cases should be recognized." He therefore shows himself to be far from an uncritical advocate of E.C.T. and it may therefore seem somewhat tendentious to submit his study to criticism. Nevertheless, the data on which he bases his conclusions

show one serious omission in that he has no adequate control group wherewith to compare his results. He has therefore, in my opinion, failed to prove how E.C.T. has altered the rate of recovery and prognosis, since he does not take into account the tendency to spontaneous recovery in depression—a factor unfortunately often suppressed or forgotten by many advocates of this form of therapy.

Dr. Jarvie's report is based on 114 cases of various types of depressive illness, but his conclusions on the effectiveness of therapy are drawn from 97 of these 114 patients, whom he regards as his "treated group." The number of convulsions administered to individuals in this series of 97 patients varied from a minimum of 2 to a maximum of 14 convulsions. The remaining 17 patients do not, however, provide an adequate control series, since Dr. Jarvie, in describing them, states that they "either did not receive E.C.T. or *received such small amounts that it was regarded as not affecting the course of the illness*" (italics are mine). One at least of these 17 received four convulsions before cardiac complications during administration dictated discontinuation of treatment. Four convulsions represent double the minimum number given in his "treated" series, and the elimination of such unsuccessful cases from the treated group obviously tends to weight the evidence in favour of E.C.T. as a form of treatment. Dr. Jarvie also does not give the time relationship between treatment with E.C.T. and recovery. Many patients submitted to E.C.T. do not show any amelioration of symptoms till some weeks or months after cessation of treatment, which gives rise to the suspicion that their recovery is not directly attributable to such treatment.

Some years ago I carried out a survey of 923 patients with a depressive illness admitted to the Royal Edinburgh Hospital for Mental and Nervous Disorders between the years 1930–48.[1] This period covered both the era preceding the introduction of E.C.T. and that following its utilization as a method of therapy. Many of the patients had been admitted on more than one occasion with recurrent depressive episodes, so that the total number of hospitalizations reviewed was 1,611. Eighty per cent. responded to a follow-up questionary by a personal visit or letter. The results of this survey—which were quite contrary to those envisaged by me at the commencement of the study—showed that (*a*) the percentage rate of recovery did not vary greatly whether patients with depression were treated conservatively or by E.C.T. Such slight differences as did exist were not statistically significant; (*b*) the use of E.C.T. did not shorten the duration of the depressive illness; and (*c*) did not prevent its recurrence. (Space does not allow of the quotation of figures, for which the original article can be consulted.)

This investigation emphasized the importance of having good control groups in the assessment of any therapy for depression, since the figures for the pre-E.C.T. era showed that 80% of the patients recovered. Of all the major psychoses, depression is recognized as having the best prognosis. An interesting finding was the considerable number of patients discharged "recovered" or "improved" within two months of admission without being submitted to E.C.T. Had E.C.T. been given as a routine measure within the first few weeks of their hospitalization, the recovery of these patients would no doubt have been attributed to its use. The clinical evaluation of E.C.T. showed that in some there was symptomatic improvement, and that recovery occurred only if treatment coincided with spontaneous recovery.

In conclusion, the findings emphasized the high expectation of recovery in depressive states and in turn underlined the necessity for the application of stringent criteria in the evaluation of any form of therapy which claims to accelerate this process of natural recovery. The need for critical review of all physical methods of treatment in psychiatry has been long overdue, and it is hoped the profession will soon undertake such a study.—I am, etc.,

Montreal, Canada. S. KARAGULLA.

REFERENCE

[1] *J. ment. Sci.*, 1950, **96**, 1060.

Galactosaemia

SIR,—Dr. B. Laurance is quite right to emphasize the frequency and possible severity of umbilical haemorrhage in babies with galactosaemia (*Journal*, February 20, p. 459), but we have no reason to suppose that bleeding from other sites is common. This possible tendency need not in any case interfere with investigations, for all blood samples that are needed can be obtained from a heel prick. We cannot agree that the diagnosis of galactosaemia can be confirmed by urine examination only. We recently investigated a 10-day-old baby with severe jaundice and a large liver. The urine contained 0.95 g.% of reducing substance, almost all being galactose. The blood sugar, however, was only 85 mg.%. Some galactose is often found in the urine of neonates; the frequency of this is at present being investigated.—We are, etc.,

F. PIERCE HUDSON.
J. T. IRELAND.

Liverpool, 12.

Medico-Legal

CARBON DIOXIDE TEST IN MURDER INVESTIGATION

The use of carbon dioxide to cause abreaction in a murder investigation was described during medical evidence at the Old Bailey last week. The trial was of Raymond Harold Barker, aged 35, an operator, who on March 4 was found guilty but insane on a charge of murdering Mrs. Beatrice Elizabeth James.

On December 15, 1953, Mrs. James was found dead at her house suffering from 60 stab wounds. A bloodstained bent vegetable knife was found in a hall-stand drawer. Barker was arrested two days later.

Giving evidence for the defence, Dr. Arthur Paterson said that Barker was suffering from mania-a-potu, and Dr. A. Rossiter Lewis said he had formed the view that Barker was suffering from manic-depressive insanity.

Replying to defending counsel, Dr. Paterson said he did not think that Barker had any control over the measure of his anger. If he was only angry with the woman he would have stabbed her in the heart or if there had been any carnal lust he would have mutilated her.

The judge said he did not follow entirely, and Dr. Paterson said there were three possibilities for a killing. One was that it was done in a state of automatism, the second that it was a sadistic attack, and the third was that he was sane and wanted to kill her. If Barker was sane at the time and simply wanted to kill the woman, then he would probably have aimed at a vital part such as the heart or the throat. In a case of lust, a man would kill a woman out of jealousy, or in a case of sexual perversion it would not be uncommon for him to rip a woman or mutilate her. The most probable explanation of the attack was that he was in a state of automatism and did not know what he was doing, because he stabbed her 60 times, only three being in vital places. He thought the state of the man's mind was due to acute alcoholism combined with a hereditary history of mental instability.

Dr. Rossiter Lewis said he decided first of all he would try to restore Barker's memory by questions, but was unsuccessful in getting details. On February 21, in the presence of the medical officer at Brixton prison, he gave Barker a mixture of oxygen and carbon dioxide (30%). Its object was to create an abreaction. It was done in two parts, the first lightly and the second more deeply, bordering on actual unconsciousness. On neither test was he able to restore the memory for the actual stabbing or what had been carried out immediately after the stabbing. His conclusion from this was that Barker's mind was so deranged at the actual time that the memory was non-existent in detailed form. "Based upon that, I came to the conclusion that at the time this offence was committed he was suffering from a form of insanity." He took the view that Barker's was a case of manic-depressive insanity which had shown itself as a result of the effect of alcohol on his brain.

Dr. J. C. McI. Matheson, principal medical officer at Brixton Prison, was called by the prosecution to give evidence of rebuttal. He said he had seen no signs of any mental abnormality. In his opinion Barker was sane at the time he killed the woman and knew what he was doing.

Dr. Desmond Curran, psychiatrist, was also called by the prosecution in rebuttal of medical evidence given by the defence.

Obituary

N. G. HORNER, M.A., M.D., F.R.C.P., F.R.C.S.
Editor, *British Medical Journal*, 1928–46

We announce with deep regret the death at the age of 72 on March 7 of Dr. N. Gerald Horner, Editor of the *British Medical Journal* from 1928 to 1946. He had been in ill-health for some time.

Norman Gerald Horner was born on January 1, 1882, at Tonbridge, Kent. His father, Arthur Claypon Horner, after serving with a Red Cross ambulance through the Franco-Prussian war, had been surgeon and naturalist to two Arctic expeditions before settling down to general practice in Tonbridge, where he was medical officer to Tonbridge School. In later years Gerald Horner used to maintain that to be born and bred in a working doctor's home was a most valuable foundation to the life and work of a medical editor. He showed an early taste for journalism, and in his schooldays at Tonbridge produced 156 numbers of a weekly comic magazine, largely written and illustrated by himself, for family circulation. From the scientific sixth form he went to Caius College, Cambridge, and graduated B.A. in the Natural Sciences Tripos of 1902. After three happy and successful years at St. Bartholomew's Hospital he qualified M.R.C.S., L.R.C.P. in January, 1906, and served a term as house-surgeon at the Westminster Hospital. On returning to Bart's as house-physician to his godfather and good friend Sir Norman Moore, he became editor of *St. Bartholomew's Hospital Journal*, of which he had already been assistant editor. Some of the many light pieces he wrote for its pages are still remembered, including "A Vision of the Second M.B.," "The Night Dresser's Dream," "The Keen Man," and "An Echo of the Past."

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About this time Sir Henry Burdett had the idea of making the *Hospital*, hitherto largely concerned with administration, into a weekly paper for general practitioners, and he persuaded Horner to write for it and to join him later as assistant editor. This occupation, with interludes of general practice in town and country, and clinical assistantships at Bart's and the Children's Hospital in Shadwell, lasted for two or three years. The technical experience in weekly journalism proved useful and led to his engagement in 1911 as assistant editor of the *Lancet* under Squire Sprigge, who had succeeded to the editorship two years before. He thus entered upon whole-time work in the office of a leading professional journal at the opening of the long-drawn-out National Insurance struggle, and he attended every one of the stormy Representative Meetings of the British Medical Association that began with the introduction of the Bill. The indoor staff of the *Lancet* were then, as now, on friendly terms with their colleagues of the *British Medical Journal*, while the close association with Squire Sprigge was full of profit and entertainment. But the proprietorship of the paper was changing hands, and the war upset things further, so that when Horner took a temporary commission in the R.A.M.C. early in 1915 he parted company with the *Lancet*. While waiting for his commission he joined the Special Constabulary and he did night duty at Buckingham Palace for a time. He served in France for two years—with No. 14 Stationary Hospital at Wimereux, with No. 36 Casualty Clearing Station and the 97th Field Ambulance on the Somme, and as registrar of No. 10 General Hospital at Rouen. In 1917 he returned to England as assistant editor of the *British Medical Journal* and began to share with Sir Dawson Williams the conduct of the paper through a period of stress and strain and of readjustment to changing circumstances. Perhaps the heaviest test during those early years came in 1920, when for five months Sir Dawson was incapacitated by the first and worst of the heart attacks that troubled him at intervals for the remainder of his life. After the lean years of the war, with their shortage of space and staff, the *Journal* gradually expanded, the *Epitome of Current Medical Literature* started again, and the editorial staff had to keep pace with reawakened activities of every kind both at the centre and locally. By the middle of 1927 it had become painfully apparent to those whose business brought them to Headquarters that advancing age and precarious health were taking heavy toll of the editor's strength. Sir Dawson Williams had lived for the *Journal* for the greater part of half a century and

shrank from the prospect of idleness; but, in accordance with arrangements made by the Council at its December meetings, he retired formally on January 18, 1928, the thirtieth anniversary of his appointment as editor, and Horner was appointed in his place.

Horner had graduated M.B., B.Ch. at Cambridge in 1910 and took the M.A. in 1919. He proceeded M.D. in 1922 with a thesis on the growth of the general practitioner in England, and read a paper before the International Congress of the History of Medicine, which met that year in London. For two sessions he was secretary of the History of Medicine Section of the Royal Society of Medicine and afterwards vice-president. At the Centenary Meeting of the British Medical Association in 1932 he opened a discussion on medical journalism in the British Empire with a paper which his friends of the *Lancet* published in the following week. The ready pen of youth was severely disciplined as time went on, so that from being fluent he became rather a fastidious writer, more concerned with lucidity and precision than he had been formerly. Beyond two short poems published during the war and a few historical papers, he wrote little after the age of 30 outside his own journal. No doubt his approach to the craft of letters was influenced by daily intimate contact for over ten years with Dawson Williams, for whom he felt a deep regard and admiration. While never trying to mould himself upon a man so different in habit of mind and intellectual texture, he nevertheless followed "the D.W. method" in the literary and business sides of an editor's work, and strove to impart this to his junior colleagues. For a piece of writing or of editorial revision he could give no higher praise than the word "workmanlike," which stood for him, as for his great predecessor, as the sovereign quality. The *Journal* certainly gained from his wide reading and constant thought and care for the English language.

Dawson Williams had been such a strong influence in the counsels of the Association for so many years, and more than anyone had been responsible for establishing the *British Medical Journal* as the outstanding general medical journal in the English-speaking world, as to make it difficult for anyone to succeed him with a feeling of equanimity. Horner had for his predecessor a deep respect which amounted almost to veneration. For years he had been Dawson Williams's right-hand man, and in one sense it can be said that even after his chief's death he still felt the force of this relationship. Extremely diffident by nature, he was almost at times too conscious of his predecessor's pre-eminence. Apart from this, when Horner succeeded to the editorship in 1928 the editorial department was in his view much understaffed, and ill-health in the small staff that there was doubled a burden that was already heavy enough. Between 1928 and 1931, three of his medical assistants had to resign because of illness, and there is no doubt that Horner felt that he could not have taken over the reins of office under greater disadvantages. It is true to say also that, rightly or wrongly, he thought the Association did not fully appreciate the difficulties under which he was then working. From 1930 onwards conditions gradually became more stable and he could be assisted by a small staff, who, under his guidance, had to gain their experience while working on the job. In 1934 the Association was able to appoint a deputy editor—the first time in the history of the *Journal* that such an appointment had been made.

During Horner's long editorship a number of important changes were effected in the management and printing of the *Journal*, all of which benefited from his help and experience, though in fact he took little part in initiating them, being by nature inclined to see in change disadvantages rather than advantages. About 1934 criticisms were voiced in different quarters about the physical appearance of the *B.M.J.* There was, for example, the sham gothic type on the cover, the rather grey effect of the printed page, the preponderance of printer's rules and other typographical devices which some described as old-fashioned. After the Journal Committee had made a preliminary survey of the situation it sought, at Horner's suggestion, the help of Mr. Stanley Morison, who was typographical adviser to the *Times*, the Monotype Corporation, and the Cambridge University Press, and the designer of the Times New Roman type. Work on the typographical reform of the *B.M.J.* extended over a period of months, and under Mr. Morison's inspiration and guidance a complete change was effected and the *Journal* appeared in its new dress on January 2, 1937. The device which has appeared on the cover since that date was designed by Mr. Eric Gill. In the discussion that went on round this subject it soon became evident that this change of format brought obviously to the front the need for a change in the method of printing the *Journal*. Up to the end of March, 1937, the Association had had its own composing room on the fourth floor of the North wing of B.M.A. House, and each week the formes were loaded on to a van in Burton Street to be taken to Fetter Lane for the final machining to be done. The *B.M.J.* must have been one of the few remaining periodicals of any size or standing which still maintained its own separate composing room. After much debate in committee and Council, the Association finally decided to dismantle its composing room and to have the *Journal* composed and printed in one and the same place. Undoubtedly this made for economy and efficiency, and speed of production, though many of the older members of the Council and, indeed, Horner himself, viewed with much regret the disappearance of the composing room of which they had every reason to be proud. When the printing works of Messrs. Eyre & Spottiswoode, who were responsible for printing the *Journal* from 1937 to 1941, were destroyed in an air raid on May 10, 1941, those responsible for the conduct of the *Journal* were relieved not to have a composing room on their hands. Monday, May 12, 1941, was a memorable day in the experience of the editorial department and, in particular, of the editor. When Horner arrived at his office on that day he and his staff were faced with the fact that they were without a printer and that blocks and type which had been prepared for that week's *Journal* had flowed down Norwich Street in a flood of molten metal. Under Horner's guidance, he and his much-depleted war-time staff gathered together bits and pieces of copy by lunch-time and by the middle of the afternoon had secured the willing co-operation of the Temple Press in Clerkenwell. A *Journal* was "made-up" by the end of the afternoon and went to press on time on the Wednesday, every member receiving his copy that week by the usual post. Horner happily christened this issue the "Phoenix Number." The risks of continuing to print the *Journal* in London were vividly brought home by this event, which at the time it was the fashion to describe as an "incident," and a decision was quickly made to transfer,

if possible, the printing of the *Journal* outside London. Horner himself had always been used to having a printer near at hand, and he was indeed dismayed at the difficulties that might arise if the *Journal* was printed outside London while it continued to be edited from B.M.A. House. When a decision was finally taken and Messrs. Fisher, Knight & Co. agreed to print the *Journal* at St. Albans, Horner had no wish to follow the printing into the relative security afforded by a town nineteen miles from B.M.A. House. To the end of the war he continued his work as editor in London.

On top of the stress and strain inseparable from an experience shared by all other Londoners, Horner had the grave misfortune, in the winter of 1942, to suffer a detachment of the right retina. He decided not to take the chance of partial recovery of sight in that eye which operation might have given him. Thereafter his health suffered and he was compelled by illnesses to remain away from work for months at a time. Nevertheless, even when in hospital he still continued to do what work he could for the *Journal*.

In spite of these difficulties—if the evidence of outside observers is to be accepted—the *Journal* gained in support and prestige throughout the war years. Not only that, but during these years it was found possible for the Association to undertake the publication of new quarterly journals. In 1939 the Association was publishing the *Archives of Disease in Childhood*, the *British Heart Journal*, and the *Journal of Neurology*. During the war, in conjunction with the Association of Industrial Medical Officers, the *British Journal of Industrial Medicine* was launched in 1944. In 1944, too, in co-operation with the Empire Rheumatism Council, it began publishing the *Annals of the Rheumatic Diseases*. It laid plans for the publication of *Thorax*, the first issue of which was published in 1946. Before the war ended a scheme was worked out for establishing an abstracting service, and *Abstracts of World Medicine* and *Abstracts of World Surgery, Obstetrics and Gynaecology* as a result of this made their appearance at the beginning of 1947. Although because of ill-health Horner was able to take little part in the initiation of these, he gave all these various projects his help, encouragement, and guidance, and was the author, for example, of the title under which the abstracting journals were finally brought out. When he retired at the end of 1946 under the age limit, he was able to pass on to his successor a *Journal* that had grown in prestige and circulation, and an editorial structure that had stood the test of time. More important still, he handed on a sound tradition of responsible editorship which he himself had inherited and had maintained intact from the corrosion that is sometimes the result of the passage of time. He was scrupulous, perhaps at times over-scrupulous—if this is, indeed, possible—in the use of the English language, and nothing could ruffle him more than an infelicitous phrase, an apparent breach of etiquette, or work that was in any way slovenly or unfinished.

Horner suffered from a sensitivity that made him vulnerable to the criticisms and attacks to which any editor of any responsible journal is always exposed. Extremely diffident by nature, he felt at times over-burdened by the responsibility of his post. Yet to the outside world he showed little of this, his philosophy being, as he used to say, that of the stoic. Of the many tributes paid to him in his career he valued above all his election as F.R.C.P. (under by-law xxxix (b)) in 1939: he was made F.R.C.S. in 1942. His attachment to the *B.M.J.* and all its fortunes was deep and abiding, and though he knew he had to retire at the age limit, to leave his office even though his health was poor was a severe wrench. To his colleagues he was unfailingly courteous and helpful. His mastery of the English language was a continuing example to them. Whatever difference of opinion there might be, Horner always remained patient, and was, above all, just and fair in his dealings.

Outside the *Journal* Horner's other strong attachment was to his club, the Savile. To meet him there was really to meet a different person—to meet someone who was a kind and considerate host and a witty and light-hearted companion. Towards the end of the war he began to live at his club and there he remained until his last illness. Above all he used to enjoy meeting there men eminent in other walks of life. He had a wide interest in literature and art, and a skill in writing that was the envy of his colleagues. It is a matter for great regret that on his retirement ill-health made him, no doubt, disinclined to put down on paper his reflections on the medical scene of which he had been for so long a detached and judicious witness. For a time after 1947 he lent a hand in the compiling of the medical history of the war, thus returning to an early interest. His wife, Grace Malleson Fearon, died in 1950. He leaves one son.

Sir ROBERT YOUNG writes: Gerald Horner was appointed assistant editor of the *Lancet* when I was a member of its staff. It was quickly apparent that he was a man with great charm of manner and a kindly personality. I came to regard him as a friend, and he was always helpful in suggestions and ideas. He was an excellent sub-editor, and I know that Sir Squire Sprigge, who was at that time the very distinguished editor, had a high opinion of him and found him a valuable and reliable member of his staff. Horner had a wide knowledge of medical matters, a keen and incisive mind, and considerable literary gifts.

His work for the *British Medical Journal* is well known to readers and to the Association, which has been very fortunate in its sequence of editors. Horner was well worthy of his place in that distinguished roll. Ill-health had for some years handicapped his activities and allowed his friends the chance of meeting him but seldom. I saw him some months ago at the Savile Club, when he greeted me in his old friendly manner and expressed his pleasure at reviving old associations. He was a good friend, and I have happy memories of him.

Professor ALAN MONCRIEFF writes: Horner set and himself maintained a high standard of medical journalism. Nearly 30 years ago he purged my early efforts of clichés and got rid of superfluous or repetitive matter. He was always kind to juniors and encouraging, although as I got to know him better I realized that he could be almost blistering if he liked. He had a very subtle and caustic wit, and loved a good verbal quip. He had indeed a real interest in words and their use. I do not think he liked committee work. He preferred to get on with his direct editorial duties, but it was sometimes surprising to realize how little of the business side really escaped his notice. He had a difficult task to follow Dawson Williams, but I should judge that he left the *Journal* at a higher standard than when he took on, with a better standing in the scientific world.

Dr. HENRY ROBINSON writes: There is no doubt that Horner's apprenticeship under, first, the late Sir Henry Burdett, editor of the *Hospital*, and then under Sir Squire Sprigge, of the *Lancet*, taught him much about the technical side of newspaper production—type, paper, format, etc.—

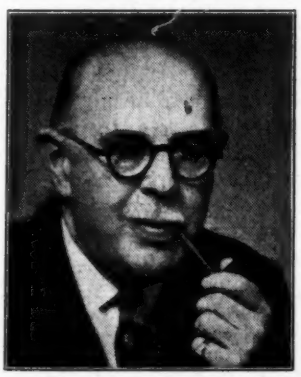
which, together with what he learned from Sir Dawson Williams later, was to prove of great service to the B.M.A. and to the *Journal* later on. At the numerous meetings of (the late) Dr. Ronald Gordon's subcommittee in 1935–6 his advice was often sought, and never in vain: he rarely intervened in the discussions unless appealed to by Gordon, but whenever he did speak his contribution was always very much to the point. The outstanding success of the reorganization which followed was due, in part, to his sage counsel and loyalty.

Horner was never a robust man, physically or constitutionally, and his many friends at the Savile noted two years ago with deep concern a gradual but steady deterioration of his health. To celebrate his seventieth birthday the members entertained him at a complimentary dinner, where poems composed for the occasion were recited in his honour —one was entitled "An Ode on a Distant Prospect of Gerald Horner." But he was already too much indisposed to make a reply such as a few years earlier would have been full of *bons mots*. A notable characteristic of the Horner touch was that his wit was never malicious and never left a sting. Though impatient of anything slipshod in the use of the English language, he was not pedantic: his appreciation of a felicitous touch or allusion in the work of his contributors or subordinates was genuine and warmly expressed.

T. JENNER HOSKIN, M.D., F.R.C.P.

By the untimely and sudden death of Dr. Jenner Hoskin on February 27, the Royal Free Hospital has lost a well-loved senior physician, its staff and students a wise and kindly friend. He was 65 years of age.

Theo Jenner Hoskin was born into a medical family on December 12, 1888, and after receiving his early education at Charterhouse proceeded to Trinity College, Cambridge, and the Middlesex Hospital, from whose medical school he graduated in 1914. After a few preliminary house appointments he joined up and served with distinction throughout the remainder of the first world war, taking part in such historic events as the landing at Suvla Bay. At one time or another he served in Egypt, Gallipoli, German East Africa, and Sierra Leone, and he was mentioned in dispatches.



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After demobilization he embarked on further post-graduate study and training, notably at the Heart Hospital, where for years he worked in association with the late Dr. Strickland Goodall. Success came with his appointments to the honorary staff of Queen Mary's Hospital for the East End and, very shortly after, in 1924, as honorary assistant physician to the Royal Free Hospital. Owing to a succession of retirements he rose unusually rapidly in seniority, and for the last 16 years of his life was senior physician to the hospital. Further appointments included that of cardiologist to St. Paul's Hospital for Genito-urinary Diseases, physician to the Royal National Throat, Nose, and Ear Hospital, and chief medical adviser to both the Pearl Assurance Company and the Friends' Provident and Century Life Office. He belonged to many learned societies: one he appreciated most was the Medical Society of London, of which he was president in 1948. The climax of his distinguished career came in the latter part of last year, when he was elected to the council of the Royal College of Physicians, an honour which gave him unusual pleasure. Not a prolific writer, he contributed from time to time to specialist journals, his words carrying both good sense and authority. One of the first papers he wrote (entitled "Five Hundred Cases of Malaria in Pensioners") was published in this *Journal* in 1921. Beyond his professional sphere he enjoyed a full and active life, being a liveryman of the Skinners Company and at one time master of the Worshipful Company of Playing Card Makers. His interest in all forms of sport was well known, and until latterly he was himself an active and keen golfer.

One of the first to appreciate the need and value of specialist departments, he speedily succeeded in building up a cardiological department in the Royal Free, deciding at the same time, in his natural humility, to limit his private patients to the cardiological field in order to give the best, and only the best, advice to both family doctor and individual patient. His art—for medicine with Jenner Hoskin was always an art rather than a science—was perhaps best demonstrated by his management of patients. Ever more interested in people than in disease, and recognizing the futility and frustration of invalidism, he had a special skill in helping the handicapped back, if not to perfect health, to as full and active a life as was practicable.

In the Royal Free Hospital he found himself for the first time in the unfamiliar surroundings of a women's medical school and training hospital. After a few hesitant teaching rounds he speedily established that attitude of easy and genial informality that lastingly endeared him both to students and to junior medical staff, while losing him nothing in respect. From then on he identified his interests with those of the hospital which he was so long to serve. He taught assiduously and skilfully and was noted both for punctuality and for regular attendance. Nothing would have ever caused him to neglect his hospital duties for private concerns. It might have been thought that the Royal Free Hospital was his life if it were not known that he brought an equal interest and enthusiasm to the claims of his wide consultant practice and to his insurance work.

He was a man of complete integrity, of unswerving high standards, and a stickler for good taste. As a colleague he was all that anyone could want and more. Unfailingly loyal, disarmingly courteous, striving to promote harmony and to discourage acrimony, exerting always a moderating influence, he became the trusted counsellor to many who knew his quality and his wisdom. The reliance placed on his judgment and experience was illustrated in this last year by his re-election as chairman of the medical committee of his hospital. Possessing a remarkable memory for people, he had the reputation of being able to name every student who had ever passed through his hands. Equal to this splendid memory was an astute and almost faultless judgment of persons, by which he managed time after time to appropriate the outstanding student for his own house-physician, sometimes to the chagrin of his colleagues. All who ever worked for him became bound in affectionate respect and thereafter could count on his continued and wholehearted support. No effort was wasted, no time ill spent, that furthered the career of his protégées.

In his home life Jenner was singularly fortunate. His wife, Maisie—daughter of Mr. William Stewart, of Skelmorlie, Ayrshire—whom he married in 1920 and who survives him, was the perfect partner, and their happy and contented home life was not only an inspiration to all who enjoyed their hospitality but provided the peaceful background essential to his restless spirit. Maisie Hoskin devoted herself completely to his interests, and not a little of his success and the freedom with which he spent his gifts and energies depended on her. To Mrs. Hoskin, his daughters Margaret and Mary, and his son, Christopher, still at his own old school, we extend deep sympathy.—U. C. L.

We are indebted to Dame LOUISE MCILROY for the following appreciation: The sudden death of Dr. Jenner Hoskin has come as a shock to all his friends, of whom he had very many. All who knew him had a great regard for him and an appreciation of his distinguished work as a physician. He devoted much of his time and skill in helping in the diagnosis and treatment of the cardiac conditions of women in pregnancy and childbirth in the Royal Free Hospital. I have always been grateful to him for the infinite trouble he took over patients not only in London but when he served on the consulting staff of the Officers' Wives Maternity Hospital at Fulmer Chase, Bucks, during the war. Dr. Hoskin always took a very personal interest in the teaching of students, and his influence on the training of young graduates was profound. His endearing personality will long be remembered. The sympathy of all his friends will go out to his devoted wife and family in their irreparable loss.

Dr. G. CATHERINE EVANS writes: Others will have written about Dr. T. Jenner Hoskin's professional and academic achievements, not only as an outstanding cardiologist, but as a physician whose breadth of vision and interests were unusually wide. Some will have mentioned his election a few months ago to the council of the Royal College of Physicians, an honour which gave such pleasure and satisfaction to his colleagues and friends. But I would like to pay tribute to his memory not only as an old student but as a patient of his for the last 34 years. Dr. Jenner Hoskin was an excellent teacher. His ward rounds were deservedly popular, for he had the happy knack of using a homely simile to impress some particular point, which consequently became indelibly printed on his students' minds. His devotion to his hospital work was unstinted, and he gave full measure in furthering the interests of the students and nurses. Every patient I sent to him without exception came back gratefully impressed by the scrupulous care and trouble he took in assessing their case. He had the gift of putting his patients quickly at their ease and giving them complete confidence in his judgment. Knowing him as his patient for so many years, I always found him to be not only a skilled clinician but a never-failing wise counsellor and kind friend.

T. W. MORGAN, M.B., B.S.

Dr. T. W. Morgan, a former member of the Council of the British Medical Association, died on February 27 in Westminster Hospital. His untimely passing at the age of 53 after a short illness is a sad blow to his many friends and patients.

Thomas Walter Morgan, who was born on June 20, 1900, received his medical training at Cardiff and at St. Thomas's Hospital, qualifying M.R.C.S., L.R.C.P. in 1927 and taking the London degrees of M.B., B.S. three years later. After a series of resident appointments at the Westminster Hospital, where he was also assistant surgical registrar and radium officer, he became a general practitioner and for twenty years conducted a large general practice in New Malden and district with exceptional ability and skill. He gave himself unsparingly to the best interests of his patients, and throughout the years was the family counsellor and friend of many of them. His efforts to bring to the aid of his patients in all walks of life, at home or in hospital, the expanding resources of modern medicine and surgery occupied nearly the whole of his time and energies; and his patients, once the first encounter with him had been successfully achieved, stuck to him with fierce loyalty. His quick and discerning mind always sought to reach the heart of any problem brought to him.

Dr. Morgan had a ready grasp of medico-political matters. His clarity of thought and happy ability to speak well in public opened to him a wide field, in which he worked hard to preserve and maintain the highest ideals of medical ethics. His energy and organizing powers were remarkable, and with these he combined a sense of humour and good fellowship which won him many friends. These gifts he put generously at the service of the British Medical Association, his local hospitals, and National Health Service committees. He was a member of the Council of the Association from 1947 to 1952 and represented his constituency at all the Annual Representative Meetings from 1942 up to last year. Among the many committees on which he served, the Central Ethical, the Private Practice, and the Health Centre Committees benefited most, in length of time, by his membership. Locally, he acted as honorary secretary of the Kingston-on-Thames Division from 1945 to the time of his death; he was chairman of the Division from 1942 to 1945; and president of the Surrey Branch in 1951–2. His work for the Kingston Victoria Hospital, of which he was chairman of the medical board for many years, brought him into nation-wide prominence and will be remembered as long as the reorganization of the hospitals under the National Health Service Act is discussed. Although he did not succeed in saving the Victoria Hospital from absorption, when the decision that it should be taken over was made he showed his sterling qualities by immediately deciding to give of his best under the new regime. Largely owing to his efforts another general-practitioner hospital now exists in place of the old Kingston Victoria Hospital.

His influence on local medical affairs was great. At the time of his death he was a Treasury medical officer, medical officer to the Borstal reception centre at Latchmere House, Ham, member of the Surrey Executive Council, and a co-opted member of the Surrey County Council's health and ambulance committee. He served the Wimbledon Hospital as an honorary physician and as vice-chairman of the medical staff committee and was vice-chairman of the Surrey Local Medical Committee. He was a past master of the freemasons' lodge at Westminster Hospital and had recently joined the Malden rotary club. During the last war, as a member of the local air raid precautions service, he was one of the first medical officers to be called into action as a result of enemy air attacks.

At the memorial service held on March 4, Christ Church, Malden, was crowded by a gathering of all his associates, representative of every section of the community in which he lived and worked. In the address a remarkable tribute was paid by his old friend, the Rev. H. E. Baldwin, and for many the memorial service lightened the shock and sense of loss of his passing, leaving instead a feeling of gratitude and encouragement from his great example. He leaves a widow and two sons, to whom we extend our deep sympathy.—J. W. S.

Medical Notes in Parliament

Service in the Colonies

Mr. JOHN TILNEY asked the Secretary of State for the Colonies on March 3 what arrangements there were for seconding doctors from the National Health Service to the service of Colonial governments; and how many were at present seconded to Nigeria and the Gold Coast respectively.

Mr. J. G. FOSTER, the Under-Secretary for Commonwealth Relations, said that hospital authorities had power to second members of their medical staffs in suitable circumstances to overseas and other posts. In addition, Health Service hospital doctors might take up employment in the Colonial Medical Service for periods up to six years, with continuing participation in Health Service superannuation. The salaries and general conditions of service of doctors so employed were similar to those for doctors on the permanent establishment. On reversion to employment in this country a gratuity was payable. One doctor was serving in Nigeria and three doctors in the Gold Coast under these latter arrangements.

Mr. TILNEY said that in Northern Nigeria there was only one doctor for every 64.000 people. He asked the Minister to discuss with the Minister of Health what might be done to make seconding better known and more popular. Mr. FOSTER agreed, and said the trouble was partly due to the recent creation of the posts and partly to reluctance to accept a new idea.

Fowl Pest Infection in Men

Mr. DENYS BULLARD asked the Minister of Health on March 4 if his attention had been drawn to the danger that four men in Norfolk might have contracted fowl pest after helping with the slaughter of chickens among which the disease had occurred. Miss PAT HORNSBY-SMITH, Parliamentary Secretary, said the Minister was advised that this disease, although in a limited sense transmissible to man, was not readily passed on among human beings. The only known clinical form of the disease in man was a mild inflammation of the eyes without constitutional disturbance. In the instance referred to the men were back at work. She added that, while it was not unreasonable to attribute the eye condition in the men concerned to contact during work with diseased fowls, laboratory tests did not confirm the association.

Consultant Service

The MINISTER OF HEALTH, having told Dr. BARNET STROSS on March 4 that all regional boards, in suitable cases, allowed transfers from whole-time to part-time medical service, was asked for his own view about this. Dr. Stross had expressed the view that the service was not best served by full-time consultants transferring to part-time. Mr. MACLEOD suggested that no such generalization could be drawn. The policy that all boards allowed transfers, subject to the needs of the service, was based on the 1948 circular, and there had been no change in that. He believed that a part-time consultant service was a very good thing, and he certainly had no evidence to show that there was any deterioration in the service provided.

Mr. A. BLENKINSOP said that some regional boards were offering the maximum number of part-time sessions, as an alternative to full-time sessions, to the greater detriment of the service. Mr. MACLEOD replied that boards might well interpret circulars, and particularly the 1948 circular, in different ways. There were different trends in different regional boards, but he had no reason to think that boards were not applying their general policy to individual cases —which was what mattered—in a reasonable manner.

Answering another question by Dr. STROSS, Mr. MACLEOD said the financial effect of such a hypothetical circumstance as the abolition of the part-time consultant service and its replacement by a full-time service could not possibly be assessed.

Dr. STROSS suggested that the saving would be considerable. Full-time consultants, he said, were not allowed any of the perquisites, such as expense allowances, of part-time service. If there could be a switchover to full-time service, would it not be possible to make the service more attractive financially? Mr. MACLEOD pointed out that matters of remuneration went back to the Spens Report. Any suggestion of abolition of the part-time service would be a breach of faith with the profession. Mr. SOMERVILLE HASTINGS said the payment for travelling time and expenses inflicted great cost on the service. The withdrawal of these facilities, which applied only to part-time officers, would save a lot of money and give the opportunity to improve the service in other ways. Mr. MACLEOD replied that he understood the point, but did not agree with it.

Mr. BLENKINSOP asked if the Minister was aware of the financial advantages enjoyed by part-time specialists employed by hospital authorities in comparison with those employed full-time, and whether he would refer the matter to the Guillebaud Committee for their consideration in view of the heavy cost of payments for travelling time and domiciliary visits charged by part-time specialists. Mr. MACLEOD replied to this that he was aware of the arrangements which were agreed in 1949. It was open to the committee to consider the point made by Mr. Blenkinsop, but it would not be appropriate for him, as Minister, to ask them to inquire into particular topics. He added in a further reply that any adjustment in terms and conditions of service was far better left to the medical Whitley Council, where it could be fully discussed.

Consultants' Salary Claim

Mrs. JEAN MANN asked the Minister of Health on March 4 what negotiations were in progress regarding salary scales to consultants, S.H.M.O.s, and registrars.

Mr. IAIN MACLEOD replied that a claim was before the Whitley Council, and the hon. Member would not expect him to make a statement while it was under consideration.

Mrs. MANN said that it had been under consideration since the Spens Report a number of years ago. General practitioners had had their pay settled under the Danckwerts award more than a year ago. Could the Minister not do something to speed this matter up, or did he enjoy the delay? Mr. MACLEOD replied that it had not been under consideration for quite as long as that, although it had been under consideration for a very long time—some 16 or 17 months, which was a very long time indeed. "I had a meeting on this subject this morning. There will be no unnecessary delay, and I think we are now nearing conclusion on the matter. . . . This is a matter of the most profound importance, which will have repercussions in many other fields."

Cotton-wool for Cushions

Five questions, concerned with the use of cotton-wool obtained under a Health Service prescription for stuffing cushions, were addressed to the Minister of Health on March 4. Mr. GEORGE JEGER, who had tabled the first three, wanted to know: (1) what action was taken against doctors who prescribed medical and surgical material without inquiring for what purpose it was required; (2) what instructions were given to doctors to ensure that they ascertained that medical supplies were necessary before they prescribed them; and (3) if he was aware that a doctor in the East Midlands had prescribed cotton-wool in large quantities, without satisfying herself of the purpose for which it was requested, and that it was afterwards used for stuffing cushions, and if he would instruct the appropriate executive committee to investigate and take action.

Mr. IAIN MACLEOD answered that a practitioner should prescribe only what was necessary for proper treatment, and if the cost of his prescribing was in excess of the amount necessary on this basis a sum might be withheld from his remuneration. "I am sure that practitioners are co-operating

in an endeavour to avoid excessive prescribing. I see no necessity for any special action in this case."

Mr. JEGER asked if the Minister would investigate this case, in which Lady Barnett, while acting as a doctor, prescribed cotton-wool in excess of the amount required; and whether any action had been taken, as she was a well-known Conservative worker, while other doctors who had prescribed cod-liver oil and malt had been fined for excessive prescribing. Mr. MACLEOD said that Mr. Jeger sought to show, on the basis of one case, that there had been abuse. What he had not said was that this happened in the autumn of 1948.

Mr. NORMAN SMITH said that this story was told by Lady Barnett a few weeks ago. Mr. HORACE KING said the Opposition had always taken the view that abuse in the Health Service could take place only with the connivance of doctors, dentists, and opticians. Was it not wrong that a Tory doctor should use her professional shortcomings as propaganda against the Health Service? Mr. MACLEOD said there was nothing in the reports he had read to justify the Opposition statements.

Dr. EDITH SUMMERSKILL asked whether the Minister did not think it would be in the interest of the Health Service for him to say that this case was unique, and that no similar case had been brought to his notice. Mr. MACLEOD said that certainly no similar case had been brought to his attention. Both he and the executive council had better things to do than inquire whether or not seven years ago a patient had or had not used appliances correctly.

Vital Statistics

Week Ending February 27

The notifications of infectious diseases in England and Wales during the week included pneumonia 869, scarlet fever 1,463, whooping-cough 2,098, diphtheria 11, measles 2,099, dysentery 910, acute poliomyelitis 24, paratyphoid fever 5, and typhoid fever 3.

Infectious Diseases

Infectious diseases were slightly more prevalent in England and Wales during the week ending February 20. The increases in the number of notifications included 183 for whooping-cough, from 1,916 to 2,099, 98 for measles, from 1,846 to 1,944, 85 for dysentery, from 669 to 754, and 62 for scarlet fever, from 1,161 to 1,223.

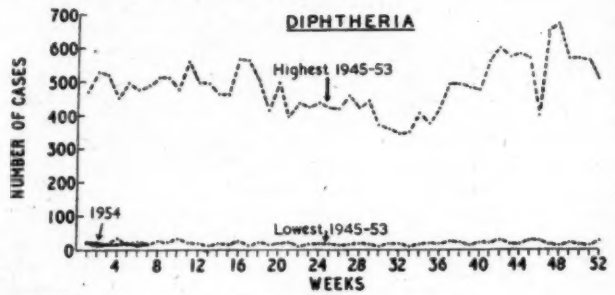
The largest variations in the incidence of measles were an increase of 58 in Norfolk, from 328 to 386, and a decrease in Cumberland, from 200 to 143. The largest fluctuation in the trends of whooping-cough was a fall of 47 in Kent, from 120 to 73. 19 cases of diphtheria were notified during the week, being 8 more than in the preceding week. The chief feature of the returns of diphtheria was a rise in Lancashire from 1 to 5. Only small variations were recorded in the local trends of scarlet fever.

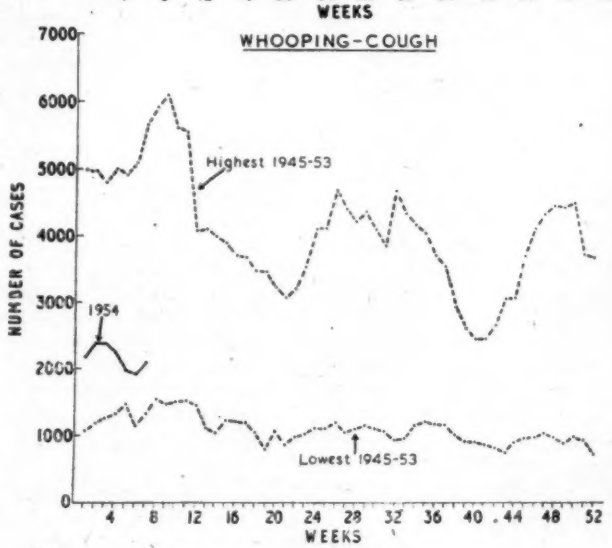
19 cases of acute poliomyelitis were notified. These were the same number for paralytic and 2 fewer for non-paralytic cases than in the preceding week. The largest returns were Devonshire 4 and Yorkshire West Riding 3. The only administrative area with more than one case was Plymouth C.B. with 4.

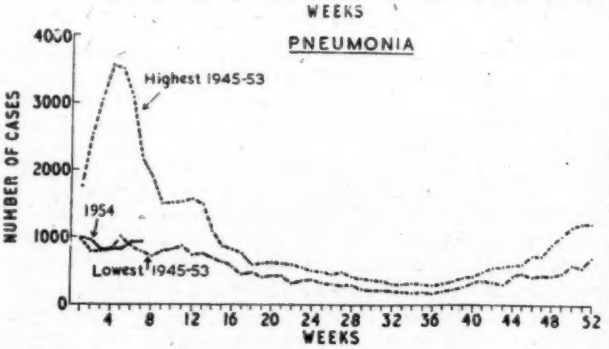
The continuous rise in the incidence of dysentery during the present year has resulted in the notifications reaching a level that has not been exceeded for almost two years. The rise during the week reviewed was mainly contributed by established outbreaks, and no new outbreak of any size was reported. The largest centres of infection were Lancashire 185 (Bolton C.B. 43, Eccles M.B. 30, Preston C.B. 23, Preston R.D. 17), Yorkshire West Riding 114 (Leeds C.B. 37, Bradford C.B. 34, Keighley M.B. 19), London 90 (Islington 31, Hackney 21), Staffordshire 68 (Cannock U.D. 52, Cheadle R.D. 10), Kent 59 (Tonbridge R.D. 19, Sevenoaks R.D. 18), Middlesex 50 (Ealing M.B. 15, Enfield U.D. 14), Norfolk 32 (Norwich C.B. 29), and Essex 25 (Walthamstow M.B. 13).

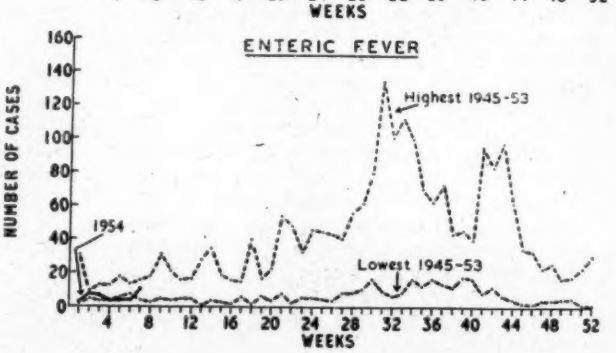
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - -, the figures for 1954 thus ———. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **February 20** (No. 7) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	19	1	5	0	1	16	2	19	0	4
Dysentery	754	90	184	9	7	241	29	136	10	
Encephalitis, acute	3	0	0	1		8	0	1	0	
Enteric fever:										
Typhoid	1	0	1	0	2	8	0	1	0	
Paratyphoid	10	0	3	0		4	0	7(B)	0	
Food-poisoning	224	18		0		194	23		0	
Infective enteritis or diarrhoea under 2 years				11	28				5	22
Measles*	1,944	29	65	10	291	32,890	1832	447	119	399
Meningococcal infection	51	8	17	2	4	63	8	28	7	2
Ophthalmia neonatorum	20	2	4	0		44	1	8	0	
Pneumonia†	932	48	262	4	1	2,142	117	475	30	17
Poliomyelitis, acute:										
Paralytic	15	0	4	0	4	25	3	2	0	2
Non-paralytic	4	0				2	0			
Puerperal fever§	225	35	4	1		258	33	8	4	1
Scarlet fever	1,223	54	187	35	24	1,550	83	264	39	73
Tuberculosis:										
Respiratory	792	98	174	33				158	29	
Non-respiratory	127	8	18	7				28	4	
Whooping-cough	2,099	71	354	50	61	2,197	121	253	29	126

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	1	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	12	0	4	0	2	9	4	1	1	2
Influenza	45	2	2	0	2	521	79	27	2	4
Measles		0	0	0	1		0	0	1	1
Meningococcal infection		2	0				4	0		
Pneumonia	421	53	29	8	13	772	109	40	10	17
Poliomyelitis, acute	1	0			0	3	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	126	20	19	1	7	151	24	34	5	7
Non-respiratory		0	0	1	1		2	0	1	3
Whooping-cough	3	0	0	0	1	9	0	0	0	0
Deaths 0–1 year	258	25	48	5	23	316	41	36	10	17
Deaths (excluding stillbirths)	7,161	1020	715	123	222	9,038	1345	808	128	206
LIVE BIRTHS	8,072	1136	963	251	460	8,047	1179	925	217	335
STILLBIRTHS	204	23	30			190	20	23		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

A Great Benefaction to Nottingham University.—Boots Pure Drug Company Ltd. has given Nottingham University £100,000 to endow two new Chairs in honour of Lord and Lady Trent. The Chairs are the "Lord Trent Chair of Pharmaceutical Chemistry" and the "Lady Trent Chair of Chemical Engineering." Lord Trent, son of Jesse Boot, the founder of Boots, has only recently resigned from the chairmanship of the company, a position he had held for 26 years. When in 1948 Nottingham University College was raised to the status of a university, Lord Trent became its first Chancellor. Before that he had been in turn a member of the University College Council (since 1923), its chairman, and in 1945 President of the College. The two new Chairs commemorate the work which he and Lady Trent have done both for the company and for the City of Nottingham. On March 3, when the gift was announced, the Court of the University heard with very great regret of the resignation of their Chancellor because of ill-health.

Annual Meeting of Irish Medical Association.—The programme for the annual meeting of the Irish Medical Association, which is being held at Killarney this year, starts with the opening of the medical exhibition by the president of the I.M.A. at 3.30 p.m. on July 6. On the next day, after religious services, there are the annual general meeting itself and in the evening the President's Reception. On July 8 and 9 there will be papers and discussions on the subjects "Drug Eruptions: Old and New," "Genito-Urinary Emergencies in General Practice," and "Recent Advances in Paediatrics." The annual dinner will be held on July 8, and a dance in aid of the Royal Medical Benevolent Fund on July 9. On the last day of the meeting, Saturday, July 10, there will be clinical demonstrations at the Mental Hospital, Killarney. Further information may be obtained from the Medical Secretary, 10, Fitzwilliam Place, Dublin.

Exchange of Teachers.—The Foreign University Interchange Scheme provides each academic year for an agreed number of visits each way between members of university staffs in the United Kingdom and those in 13 other European countries. The purpose of the visits is to promote academic contacts and to facilitate the exchange of information about recent research. The cost is shared equally between the participating countries, and in Britain the scheme is administered by the British Council. Among the medical teachers visiting Europe this month under the scheme are Professor J. McMichael from the Postgraduate Medical School, London (to Vienna, Graz, and Innsbruck universities), and Professor J. H. Burn, professor of pharmacology at Oxford (to the universities of Louvain and Liége).

Special Number of "Family Doctor."—The March issue is a bumper number to coincide with the venture of taking a *Family Doctor* stand at the Daily Mail Ideal Home Exhibition. Apart from the bright reader-winning picture of a baby on the cover, there are 49 pages of text and 58 pages of advertisements in this issue, and the whole magazine shows a high professional finish which should put it on good competing terms with its rivals. The principal medical articles are those by Sir Allen Daley on preventive medicine, Dr. Walter C. Alvarez on "How to Live with Your Blood Pressure," Dr. Greville Park on rashes, Dr. T. Traherne on schizophrenia, and Dr. G. K. Selborne on the psychology of breast-feeding. Other attractive features are an opening article by Elizabeth Bowen, the novelist, and a useful six-page guide to the keeping qualities of various foods at room temperature or in the refrigerator, ice-chest, or deep-freeze. *Family Doctor* costs 1s. 6d., and is published every month.

Royal College of Surgeons in Ireland.—On the occasion of the Charter Day Dinner of the Royal College of Surgeons in Ireland on February 13, the President, Mr. M. P.

Burke, conferred the Honorary Fellowship of the College on Sir Cecil Wakeley, President of the Royal College of Surgeons of England. The introductory oration was delivered by Mr. William Doolin, Secretary and Councillor.

Chair of Biochemistry at Oxford.—Sir Rudolph Peters, F.R.S., is retiring from the Whitley Professorship of Biochemistry at Oxford at the end of September. Applications for the chair are invited, not later than April 29, in the March 4 issue of the *Oxford University Gazette*. Sir Rudolph Peters, who will be 65 next month, is particularly noted for his studies on vitamin B_1 which paved the way for his work on arsenic poisoning and the discovery of B.A.L.

Dr. Daniel Merlin Pryce, reader in morbid anatomy at St. Mary's Hospital Medical School, has been appointed to the London University chair of morbid anatomy tenable at St. Mary's. Dr. Pryce will take up his appointment on October 1 in succession to Professor W. D. Newcomb.

Basildon and District Medical Society.—This society held its inaugural meeting recently. Any doctor interested in joining the society should get into touch with the honorary secretary, Dr. John Z. Garson, 48, Worthing Road, Laindon.

Dr. T. M. Ling, who led the B.M.A. mission to Latin America in 1951 (*Journal*, April 5, 1952, p. 756), has been made a Member of the Order of Carlos J. Finlay by the President of Cuba.

COMING EVENTS

Professor Max Rosenheim will deliver the Oliver-Sharpey Lectures on March 16 and 18 at 5 p.m. at the Royal College of Physicians. His subject will be "The Treatment of Severe Hypertension."

Christian Medical Fellowship.—The Fellowship will hold an open meeting on March 16 at 8.15 p.m. in the hall of the Royal Empire Society, Northumberland Avenue, London, W.C.1. The chairman will be Sir James Paterson Ross and the speaker Dr. D. Martyn Lloyd-Jones. Further details may be obtained from the Secretary of the Fellowship, 39, Bedford Square, London, W.C.1.

London Marriage Guidance Council.—A course of five lectures on marital problems for postgraduate medical students is being held at the Royal College of Nursing, Henrietta Place, Cavendish Square, W.1, weekly on Wednesday evenings at 7 p.m., starting on March 17. The speakers are Dr. P. L. Backus, Dr. Ethel Dukes, Dr. Clifford Allen, Dr. Philip M. Bloom, and Dr. H. V. Dicks. The fee is one guinea, and applications for enrolment should be made without delay to the Secretary, London Marriage Guidance Council, 78, Duke Street, Grosvenor Square, London, W.1.

The United Hospitals' Festival Choir.—A special performance of the *Messiah* will be given at the Royal Albert Hall on March 23 at 7.30 p.m. Tickets at 10s., 7s. 6d., 5s., and 3s. 6d. are available from the Royal Albert Hall and the usual agents.

London Medical Orchestra.—The orchestra will give its first musical evening for members of the medical and dental professions, and their friends, at B.M.A. House on April 3 at 8 p.m. The programme will include a rarely heard oboe concerto by Haydn, a concert aria by Mozart, and Schubert's Unfinished Symphony. Admission will be by programme obtainable at the door, price 2s. 6d.

The Boat Race.—Messrs. Vitamins Ltd. announce that they have available a number of tickets for doctors who may wish to view the Boat Race on April 3 from the Bemax premises. Early application should be made to Dept. B.R.1, Vitamins Ltd., Upper Mall, Hammersmith, London, W.6.

Course in Child and Family Psychiatry.—The department of child psychiatry, Ipswich Group Hospitals, offers a refresher course for school medical officers and other medical practitioners from April 5 to 9 inclusive. There is no fee. Places in the course will be allocated in order of application to 11, Fore Street, Ipswich.

Brompton Hospital Association.—The third dinner of the association will be held on April 23 at the Waldorf Hotel, Aldwych, London, W.C.2, at 7.15 for 8 p.m. Dr. A. Hope Gosse, the president, will be in the chair. The cost of the dinner will be 25s., and as accommodation is limited early application is advised. Informal dress.

NEW ISSUES

Abstracts of World Medicine.—The March issue (Vol. 15, No. 3), which is now available, contains abstracts of important papers drawn from medical and other scientific journals published in some 20 different countries and in all five continents. The subjects covered range over the whole field of clinical medicine and include pathology, pharmacology, and chemotherapy; there are also sections dealing with public health, industrial medicine, forensic medicine and toxicology, anaesthetics, radiology, and the history of medicine.

Issued monthly; annual subscription £4 4s., single copy 8s. 6d.; a specimen will be sent free on request.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Applications should be made first to the institution concerned.

Monday, March 15

●HUNTERIAN SOCIETY.—At Talbot Restaurant, 64, London Wall, E.C., 7 for 7.30 p.m., dinner meeting. Discussion to be opened by Professor L. P. Garrod and Dr. G. B. Mitchell-Heggs: The Misuse of Antibiotics.

Tuesday, March 16

HARVEIAN SOCIETY OF LONDON.—At Royal College of Surgeons of England, 8 p.m., Harveian Lecture by Dr. A. H. Douthwaite: Problem of Duodenal Ulceration.

ILFORD MEDICAL SOCIETY.—At King George Hospital, Ilford, 8.45 p.m., Dr. H. C. Faulkner: Group Practice.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. Wade: Treatment of Epithelioma of the Skin.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Oliver-Sharpey Lecture by Dr. M. L. Rosenheim: Treatment of Severe Hypertension.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE: EDINBURGH BRANCH.—At West Medical Theatre, Edinburgh Royal Infirmary, 5 p.m., annual general meeting Dr. C. A. Hopkins, Ph.D.: Filariasis in the West African Rain Forests

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Mr. Aleck W. Bourne: Restraint in Obstetrics.

SOUTH WEST LONDON MEDICAL SOCIETY.—At Bolingbroke Hospital, Wandsworth Common, S.W., 8.30 p.m., Dr. P. A. B. Raffle: Uses of Medical Statistics.

WEST END HOSPITAL FOR NERVOUS DISEASE.—5.30 p.m., neurological demonstration by Dr. C. C. Edwards.

Wednesday, March 17

●FACULTY OF ANAESTHETISTS: ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Joseph Clover Lecture by Dr. T. Cecil Gray: Disintegration of the Nervous System.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Precancerous Conditions of the Skin.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. J. G. Sandrey: Vesical Neoplasms.

LIVERPOOL MEDICAL INSTITUTION.—At David Lewis Northern Hospital, Liverpool, 3 p.m., clinical meeting. Symposium on Diabetes.

●LONDON MARRIAGE GUIDANCE COUNCIL.—At Royal College of Nursing, 7 p.m., Dr. P. L. Backus: Psychology of Marital Adjustment.

MIDLAND MEDICAL SOCIETY.—At Birmingham Medical Institute, 8.15 p.m., Dr H. F. Humphreys: Magic and Medicine.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Joseph Clover Lecture by Dr. T. Cecil Gray: Disintegration of the Nervous System.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Miss Isabel Macdonald, S.R.N.: Royal Nurses in History.

ROYAL MICROSCOPICAL SOCIETY.—5.30 p.m., Dr. F. J. Aumonier: Regeneration of Striated Muscle Following Coxsackie Infection.

●ROYAL SOCIETY OF ARTS.—2.30 p.m., Trueman Wood Lecture by Dr. E. D. Adrian, O.M., P.R.S.: Recent Developments in the Study of the Sense Organs (illustrated by lantern slides).

Thursday, March 18

BRITISH INSTITUTE OF RADIOLOGY.—8 p.m., Mr. D. Innes Williams: Urinary Obstruction in the Early Years.

●CHARING CROSS HOSPITAL MEDICAL SCHOOL.—5.30 p.m., Huxley Lecture by Sir Lionel Whitby: Dynamics of Haemopoiesis.

EDINBURGH CLINICAL CLUB.—At 7, Drumsheugh Gardens, 8 p.m., Dr. John Thomson: Care of the Neonatal Infant.

INSTITUTE OF PSYCHIATRY.—5 p.m., Dr. G. M. Carstairs: Attitudes to Death and Suicide in an Indian Cultural Setting.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., discussion: Minor Injuries of Joints. Opener, Sir Reginald Watson-Jones.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.30 p.m., Dr. F. Avery Jones: Clinical Problems of Gastroenterology.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., special university lecture by Professor A. C. Lendrum: Pulmonary Changes due to Cardiac Disease.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Oliver-Sharpey Lecture by Dr. M. L. Rosenheim: Treatment of Severe Hypertension.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At Royal Army Medical College, 7.30 p.m., laboratory meeting. Demonstrations.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., psychiatry demonstration by Sir Paul Mallinson.

UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL.—At Lecture Theatre, 5 p.m., Sydney Ringer Memorial Lecture by Professor G. L. Brown, F.R.S.: Studies on the Sympathetic Nervous System.

Friday, March 19

BRITISH INSTITUTE OF RADIOLOGY.—5 p.m., meeting of medical members.

FACULTY OF RADIOLOGISTS: RADIODIAGNOSIS SECTION MEETING.—At Royal College of Surgeons of England, 2.15 p.m., Dr. Roy Astley and Dr. J. W. Gerrard: *X*-ray Diagnosis of Coeliac Disease; Dr. R. E. Steiner and Dr. Ian Donald: Respiratory Diseases in the Newborn.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. L. Forman.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Professor R. A. Willis: Metaplasia.

Saturday, March 20

BIOCHEMICAL SOCIETY.—At Department of Biochemistry, University College, 10.45 a.m., A.G.M. followed by scientific papers.

APPOINTMENTS

DRUMMOND, R. GORDON, M.B., Ch.B., D.P.H., Medical Officer of Health for the City of Durham, Durham Rural District, Brandon and Byshottles Urban District, and Assistant County Medical Officer, Durham County Council.

DUNN, MICHAEL J., M.B., Ch.B., Assistant County Medical Officer and School Medical Officer to the Isle of Ely County Council, March, Cambridgeshire.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—C. R. Savage, M.B., B.S., F.R.C.S., Part-time Surgical Registrar; Gwendolyn R. Tapp, M.B., B.S., D.C.H., Assistant Resident Medical Officer, Tadworth Court.

LIVERPOOL REGIONAL HOSPITAL BOARD.—A. V. Clemmey, B.M., B.Ch., D.O.M.S., Part-time Assistant Ophthalmologist to hospitals in the Warrington area; W. M. Owen, F.R.C.S., D.L.O., Part-time Consultant Ear, Nose, and Throat Surgeon, St. Helens area.

NORTH-EAST METROPOLITAN REGIONAL HOSPITAL BOARD.—J. W. Lewis, M.B., B.S., D.A., Part-time Anaesthetist (Consultant), Harts Hospital, Woodford Green; E. Hacker, M.R.C.P., D.A., Part-time Anaesthetist (Consultant), St. Andrew's Hospital, Bow, and St. George-in-the-East Hospital, Wapping; Sheila Millar-Danks, M.B., B.S., D.A., Part-time Anaesthetist (Consultant), St. Andrew's Hospital, Bow; C. D. Wilson-Sharp, M.B., B.S., D.M.R.D., Full-time Radiologist (Consultant), Colchester Group of Hospitals; A. Giordani, M.R.C.S., L.R.C.P., D.M.R.D., Part-time Radiologist (Consultant), King George Hospital, Ilford; Ella Preiskel, M.B., B.S., D.M.R., Part-time Radiologist (Consultant), St. Mary's Hospital, Plaistow, and Forest Gate Hospital.

ROTH, MARTIN, M.D., M.R.C.P., D.P.M., Visiting Director, Laboratory of Experimental Therapeutics, Allan Memorial Institute of Psychiatry, McGill University, Montreal, until September 1, 1954.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—L. C. Bell, M.B., B.Ch., B.A.O., F.R.C.S., Senior Registrar, Department of Thoracic Surgery, Frenchay Hospital, Bristol; R. R. Knowles, M.B., B.S., D.P.M., Senior Registrar in Psychiatry, Bristol Mental Hospital; Beatrice E. Sleigh, M.B., Ch.B., D.A., Anaesthetic Registrar, Frenchay Hospital, Bristol; E. A. W. Houghton, M.B., Ch.B., Medical Registrar, Southmead Hospital, Bristol.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Bauer.—On February 25, 1954, to Gitta, wife of Jacob Bauer, M.D., a son—Eran Nicodemus.

Donohoe.—On February 26, 1954, at The Firs, Mansfield Road, Nottingham, to Ursula Donohoe (formerly Wilkin), wife of Dr. T. W. G. Donohoe, a sister for Mollie.

Radeski.—On February 16, 1954, at the Middlesex Hospital, London, W., to Lois, wife of Carl Radeski, M.B., B.S., of the Repatriation General Hospital, Concord, New South Wales, Australia, a daughter—Carole.

DEATHS

Deane.—On February 20, 1954, Reginald Neville Deane, M.B., B.Ch., of 2, Canterbury Road, Croydon, Surrey.

Douglas.—On February 18, 1954, at Old Manse, Lockerbie, Dumfries, John Primrose Douglas, M.B., Ch.B.

Gibson.—On February 18, 1954, at The Gables, Grimsby Road, Cleethorpes, Lincs, Robert Ernest Stewart Gibson, M.B., Ch.B.

Grills.—On February 16, 1954, at Craybrow, Whitbarrow Road, Lymm, Cheshire, Galbraith Hamilton Grills, M.D., aged 82.

Hues.—On February 13, 1954, at Lobden Cottage, Colwall, Malvern, Worcs, Herbert Walter Hues, L.S.A.

Jeffery.—On February 11, 1954, at his home, Sandon House, Heywood, Lancs, Harry Foster Jeffery, M.B., Ch.B., J.P.

Jeffrey.—On February 21, 1954, at 24, Stevenson Street, Dalmuir, Dunbartonshire, John Edward Jeffrey, M.B., Ch.B.

McKay.—On February 8, 1954, at the General Hospital, Burnley, Lancs, Charles McKay, M.B., C.M., of The Lindens, Manchester Road, Burnley.

Marrable.—On February 22, 1954, at the Cambridge Hospital, Aldershot, Hants, Arthur Trevor Marrable, D.S.O., M.R.C.S., L.R.C.P., Lieutenant-Colonel, R.A.M.C., aged 44.

Melville.—On February 10, 1954, at 20, Hornsey Rise, London, N., William Spence Melville, M.B., Ch.B.

Miles.—On February 11, 1954, at Bewdley, Worcs, Usher William Newton Miles, M.R.C.S., L.R.C.P., aged 82.

Mitchell.—On February 19, 1954, at 22, Warrender Park Terrace, Edinburgh, James Mitchell, L.M.S.S.A.

Nightingale.—On February 12, 1954, at Uppingham, Rutland, John Nightingale, M.D., D.P.H., Lieutenant-Colonel, R.A.M.C., T.D., retired.

Porter.—On February 4, 1954, at the City Hospital, Exeter, Arthur Edward Porter, M.D., D.P.H., late of Budleigh Salterton, Devon, aged 80.

Reid.—On February 8, 1954, at Dunmar, Tigh-na-brauich, Argyll, Spence Daer Reid, M.B., Ch.B., Colonel, late R.A.M.C., retired.

Rogers.—On February 9, 1954, at 4, Queensborough Studios, London, W., Frederick Colin Rogers, M.R.C.S., L.R.C.P., Lieutenant-Colonel, I.M.S., retired.

Sweet.—On February 16, 1954, at Westholme, 10, Victoria Drive, Troon, Ayrshire, Robert Sweet, D.S.O., M.B., Ch.B., F.R.F.P.S., Colonel, I.M.S. (retired), aged 66.

Webster.—On January 16, 1954, at 75, Sandon Road, Birmingham, Kathleen Mary Webster, M.R.C.S., L.R.C.P., D.P.M., late of Whitley Bay, Northumberland.

Wynne.—On February 7, 1954, at Midhurst, Avenue Gardens, Cliftonville, Kent, Albert Edward Wynne, M.D., F.R.C.S.I., formerly of 27, Westland Road, Dublin, aged 88.

Any Questions?

Intradermal T.A.B.

Q.—*An American textbook of preventive medicine refers to immunization with T.A.B. by the intradermal route. Is this an effective route for inoculation, and are there any special hazards? Is it recommended for routine use?*

A.—Vaccination against the enteric fevers by intradermal inoculation of T.A.B. vaccine has been studied particularly by American investigators, who have shown that the antibody response is essentially equal to, or even greater than, that obtained following subcutaneous inoculation, even when the dosage is markedly reduced. However, it was considered that this method was more suitable as a booster injection in previously immunized persons rather than a method for primary immunization. The recommended dose is 0.1 ml., and there do not seem to be any associated risks. Intradermal inoculation is seldom used in this country, but may be useful for people who have reacted severely to previous subcutaneous injections.

Deep Anaesthesia for Domiciliary Midwifery

Q.—*I use a standard gas–oxygen machine for domiciliary maternity work. For forceps deliveries a vaporizer is plugged into the gas circuit, containing either "vam" (25% vinyl ether with 75% ethyl ether, by weight) or trichlorethylene according to whether any source of ignition is present. Vam gives much more satisfactory operating conditions, but is often contraindicated owing to open fires; trichlorethylene has to be "pushed" for anything but easy outlet forceps deliveries, and then the recovery period is undesirably long. Is a small dose of intravenous pethidine (25 mg.) combined with gas and oxygen in any way contraindicated for this sort of situation? Alternatively, is any other technique recommended for use when there is a definite explosion risk? Positive pressure is available but no suction, so relaxants are too dangerous to use.*

A.—Only the most simple obstetric operations should ordinarily be carried out in the patient's own home, and for these the type of anaesthesia mentioned in the question should be adequate. Any complication or situation calling for deeper anaesthesia is generally an indication for transferring the patient to a fully equipped maternity hospital. There are a few exceptions to this rule; manual removal of the placenta, for example, should be carried out wherever the patient is situated.

In the event of an additional anaesthetic agent being required in domiciliary practice, then the question arises as to its object. If more relaxation of the muscles of the pelvic floor and vagina is required, local infiltration or pudendal block with an analgesic solution followed by episiotomy is safe, effective, and easy. If, however, the object is to relax the uterus in order to rotate the foetal shoulders or to remove an imprisoned placenta, then the most suitable anaesthetic is probably open ether. Indeed, there is much to be said for using this as a routine rather than the gas, oxygen, and trichlorethylene mixture mentioned in the question.

The risk of fire and explosion should be eliminated not by recourse to an anaesthetic agent which involves other dangers, but by removal of the fire. If the practitioner is dealing with booked cases he might advise all his patients antenatally against having a fire (other than one easily extinguished) in the room during labour. If he is called to an emergency case in which he has had no opportunity to give this advice, then it is not a difficult matter to clear the fireplace with a shovel and bucket.

Women vary considerably in their sensitivity to pethidine, and even a small dose given intravenously can have a major effect, especially if other forms of anaesthesia are in use

at the same time. The margin of safety is increased if pethidine is given in dilute solution and in divided doses—or even in the form of a drip infusion. This sort of complicated procedure is, however, clearly unsuited to domiciliary midwifery. Likewise, as the questioner suggests, relaxant drugs have no place. Safety demands that these be given only by an expert working under hospital conditions. Moreover, their application to obstetric operations is limited. They promote relaxation of pelvic floor muscles, but this can be more safely achieved by local analgesia. They do not, however, relax the uterus, and for this reason they may hinder rather than help obstetric manœuvres. Moreover, they appear to encourage silent regurgitation of stomach contents, probably by relaxing the diaphragm. Since they also suppress the cough reflex, they increase the risk of inhalation asphyxia and pneumonia.

It remains to be added that many obstetricians still hold the view that chloroform, if properly administered on an open mask with no gamgee to interfere with a generous intake of air, still has a place in domiciliary midwifery. Those who have been trained to use it will probably regard it as the obvious and simple solution to the problem posed in the question. It should not, however, be given for more than a short period of time, nor should its administration be repeated. It is also to be avoided if labour has been much prolonged and if the patient shows evidence of ketosis.

Mepacrine Stains

Q.—*How can mepacrine stains be removed from clothes?*

A.—Mepacrine stains are chemically similar to proflavine stains, and in his book on the acridines Albert[1] says that stains on fabrics can be lightened by washing with alcohol until no more colour is removed; the residual stain should then be smeared with oleic acid and immersed in alcohol containing a small amount of ammonia. Probably the simplest procedure of all, which might be tried first, is to rub the stain with 1% ammonia and then treat it with 80% alcohol. This should remove it.

REFERENCE

[1] *The Acridines*, 1951. Arnold, London.

Should Mothers Leave their Babies?

Q.—*Is it psychologically harmful to leave a baby of 6 to 12 months with its grandparents while its parents are away for a month?*

A.—Some interesting observations have been made, especially by Dr. John Bowlby, on the emotional reactions of young children removed from their mothers—for example, when they have had to go into hospital. These reactions not only occurred while the child was away but also after his return home. Apart from the anxiety and estrangement which one might expect, a variety of behaviour disorders were also seen. Bowlby found that the age of greatest susceptibility to such reactions was rather older than in the case described in the question, 18 months to 2 years being the peak. Control studies and more prolonged follow-up than has so far been possible are needed to show just how seriously these reactions are to be taken. Until further work brings greater understanding, practical problems are best solved in a common-sense way.

Thus in the case described it is unlikely that any harm would arise to the child. The period of parental absence is short, and the child should be able to get over it quickly. Furthermore it is very young, and at that stage of development, apart from being less aware and less discriminating than a child of 2, is unlikely to have the fixation on one person which it would normally have later. The most important psychological needs of a young child, affection and security, will presumably be supplied by the grandparents, and any severe emotional reaction during or after its stay with them is improbable. It is the anonymous atmosphere of a hospital or institution which appears to be deleterious.

Mercury Poisoning in Dentists

Q.—*Is there any evidence that the habit of some dentists of mixing amalgam filling material in the palm of the hand may, in the course of years, cause symptoms of chronic mercurial poisoning?*

A.—While theoretically the danger does exist, there does not appear to be any case reported where chronic mercury intoxication has arisen in a dentist in the way suggested by the questioner. The work of Storlazzi and Elkins[1] tends to show that some mercury absorption does occur from newly inserted silver-amalgam fillings. But the maximum temporary concentration is less than that found continuously in the urine of workers exposed regularly to quantities of mercury apparently too small to cause chronic poisoning. However, symptoms of mild chronic mercury poisoning are difficult to distinguish from irritability and anxiety due to other causes, and often have to be sought for specifically. In short, the risk to dentists, though theoretically real, must be very small indeed—if it exists at all.

REFERENCE

[1] *J. Industr. Hyg.*, 1941, 23, 459.

Dry Heat Sterilization in General Practice

Q.—*What are the disadvantages of dry heat sterilization in general practice? Is it suitable for sterilizing suture materials and dressings? Could a domestic electric oven be used for the purpose?*

A.—Dry heat sterilization is unsuitable for either of these purposes; it is indicated only for syringes, glassware, powders, and oils. Any fabric (dressings or thread, the latter being presumably the form of suture material meant) is charred and rendered brittle. Any oven which attains *throughout* (temperature may vary by many degrees in different parts) a temperature of 160° C. will serve: 180° should not be exceeded. The melting point of the solder used on syringes and needles is about 200° C., so any higher temperature than this would cause the solder to flow and the mounts to separate. A suitable thermometer would decide whether the oven in question is suitable. Most cooking ovens normally attain too high a temperature, but when regulation is possible they may be used.

NOTES AND COMMENTS

Smoking Cures.—Colonel H. W. DAUKES (Bethnal Green Hospital, London, E.2) writes: With reference to your answer to the question on smoking cures ("Any Questions?" February 20, p. 471), I feel that the answer given, while correct, is not very helpful. I have found a really good way to cut smoking *down* easily and effectively without undue nervous strain. Having lived much abroad, I developed the habit of smoking about 35 cigarettes a day regularly over many years. On returning to this country I found I could not afford this, so I tried making my own cigarettes first with a "rizla"-type maker; then, when I found this was effective, with one of the box type in which the closing lid rolls the cigarette, using a filter tip (mainly to give a neat end to the cigarette) and only making a cigarette when I actually wanted to smoke one. I have cut down to half an ounce of tobacco a day, which, when added to the cost of the filter tips and paper, results in a saving of £70 per annum. The two most important points are: (1) Not to sit down and roll a whole batch of cigarettes but only to make one when actually wanted—this cuts out a large number. (2) When you can have a cigarette whenever you want it sufficiently to go to the trouble of making it, this cuts out any element of nerve strain.

All communications with regard to editorial business should be addressed to The EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.
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